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TO TREAT THE PATIENT AS WELL AS HIS ANGINA

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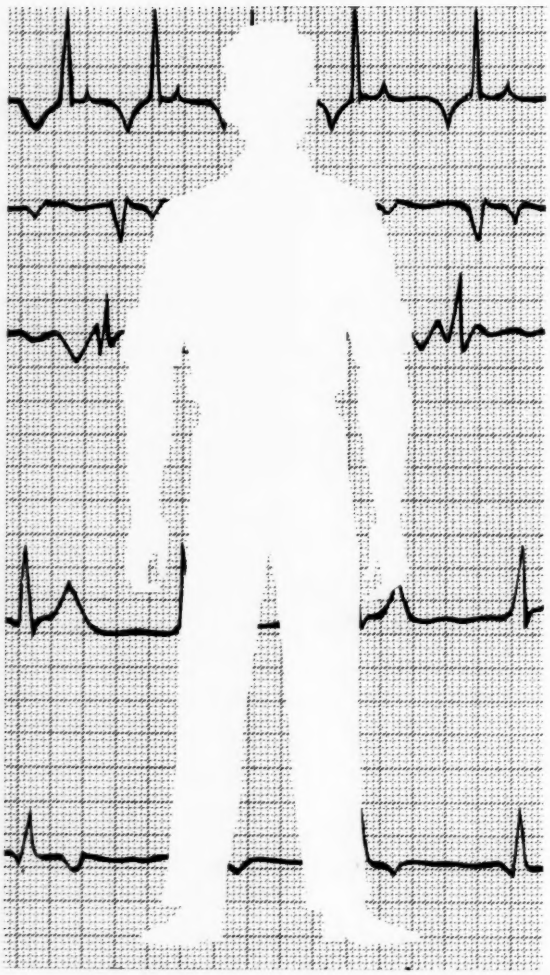
for the patient with Angina



FOR THE ANGINA

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PERI 548

STARVATION AND OPERATION

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Ch.M.Edin., F.R.C.S.E., F.R.C.S.
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From the Department of Surgery, University of Aberdeen

WHEN after partial gastrectomy the intake of water is stopped for 2 days, and that of food for 4 days, there is usually a large and rapid loss of weight (Wilkinson 1956). This loss is greatest during the first 24 hours after operation, and the suggestion was made that its main component was water lost insensibly and in the urine. To test this possibility four healthy adult male student volunteers were subjected to the same programme of restriction of water and food as the patients, and the resulting changes in body-weight and urinary excretion have been compared with the earlier findings after partial gastrectomy.

Methods

After a preliminary period of urine collection, the four volunteers did not drink for 48 hours or eat for 4 days. Like the patients, they were given on the 3rd day 720 ml. and on the 4th day 1440 ml. of distilled water, and on the 5th day they resumed an unrestricted diet. The daily periods began at noon; urine was collected in 6-hourly specimens using chloroform as a preservative. The analytical methods were the same as those previously described. The volunteers were not confined to bed but remained in a side ward for most of the period of study in similar environmental conditions to the patients. The second 6-hour specimen from subject A was lost after it had been collected and the volume had been measured, but before it was analysed.

Results

Urinary Excretion

The *volume of urine* passed in each 24 hours is shown in table I. The ability to reduce the volume of urine varied widely, but it is notable that so little was passed on the 4th day when the water intake had been raised to 1440 ml. per 24 hours. There was little difference in the average total volume passed in 4 days by the controls and the patients, but the onset of oliguria was in general more rapid and intense after operation. The large variations in volume between the controls on the 1st day were probably mainly due to differences in intake during the 24 hours just before the fast began. In spite of this, the total amounts of urine passed during the 4 days of the experimént by three subjects varied over a range of only 150 ml. in 3000 ml.; the fourth subject passed 400 ml. less than the average for the other three subjects.

Sodium and potassium.—The fall in the output of sodium in the urine was slower and smaller in the volunteers, who lost more than twice as much in 4 days as did the patients (tables II and III).

The volunteers conserved sodium efficiently from 48 to 72 hours after the intake was stopped, and the sodium output in the urine rose within 24 hours of the resumption of an unrestricted intake of food.

The volunteers did not show any increase in potassium output during the first 48 hours, as the patients did after operation, and the average potassium loss in starvation was only two-thirds as great as after operation. There was more variation in the individual outputs of sodium and potassium than there was for water.

Nitrogen.—The total urinary excretions of the four subjects during the four days were (A) 47·28 g., (B) 57·4 g., (C) 59·26 g., and (D) 57·31 g.; one specimen of urine from A having been lost. The average daily excretion was 13·44 g. There was no increase in the urinary nitrogen excretion such as occurs within 48 hours after an operation like a partial gastrectomy.

Thirst.—All volunteers experienced thirst which was most severe during the second 24-hour period and was then accompanied by dryness of the mouth. When during the third 24-hour period the consumption of water was resumed it was welcomed, but during the 4th day the appetite for water was satisfied by less than the hourly quantity which was allowed.

Body-weight

There was a difference in body-weight between the volunteers, whose weights varied from 68·75 to 85·0 kg. (average 78·16 kg.) and the fifteen patients who were earlier observed after various operations, whose weights varied from 45·1 to 68·4 kg. (average 56·81 kg.). The changes in weight after operation and during starvation by the volunteers have been expressed as percentages of the initial body-weight (table IV and figure). Although the average weight loss of the volunteers was less than the average loss of the patients after operation there was some individual variation. There is no satisfactory explanation of the larger weight loss of C. Three of the four

TABLE I—URINE VOLUME (ml.) IN 4 CONTROL SUBJECTS

Day	−2	−1	1	2	3	4	5	6	Total days 1–4
Intake	unrestricted		0	0	720	1440	unrestricted		2160
Subject									
A	1415	780	1160+	575	640	685	1025	810	3060
B	..	..	1170	555	550	650	865	665	2925
C	2585	1720	940	685	815	635	940	880	3075
D	3090	1065	465	785	700	650	950	1470	2600
Daily average Controls	..	..	934	636	676	650	942	966	2915
Daily average Patients	..	..	645	563	743	933	912	915	2884

TABLE II—URINARY EXCRETION OF SODIUM (mEq.) IN 4 CONTROL SUBJECTS

Day	−2	−1	1	2	3	4	5	6	Total days 1–4
Intake	unrestricted		0	0	0	0	unrestricted		0
Subject									
A	216	99	134+	70	46	36	16	108	286
B	..	..	101	122	63	39	5	21	325
C	204	197	152	121	70	30	22	127	373
D	201	196	85	152	35	12	34	121	284
Daily average Controls	..	..	118	116	53	29	19	94	317
Daily average Patients	..	..	74	32	17	22	28	35	145

TABLE III—URINARY OUTPUT OF POTASSIUM (mEq.) IN 4 CONTROL SUBJECTS

Day	−2	−1	1	2	3	4	5	6	Total days 1–4
Intake	unrestricted		0	0	0	0	unrestricted		0
Subject									
A	68	68	27·5+	40	36	37	29	47	134
B	..	..	33	49	63	51	54	69	197
C	68	92	63	56	64	53	40	84	236
D	88	102	33	43	56	43	38	66	175
Daily average Controls	..	..	39	47	54	46	40	66	185
Daily average Patients	..	..	89	80	56	54	40	35	279

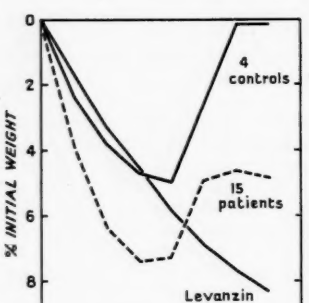
TABLE IV—DAILY CHANGE AS PERCENTAGE OF INITIAL WEIGHT IN 4 CONTROL SUBJECTS

Subject	Initial weight (kg.)	Daily change (% of initial weight)						
		1	2	3	4	5	6	7
A	77·7	−1·64	−1·6	−0·53	−0·18	+2·7	+2·6	−0·82
B	85·0	−2·4	−0·91	−0·86	−0·54	+0·54	+3·43	+0·03
C	68·75	−2·73	−2·2	−1·58	−0·53	+3·6	+3·09	+0·16
D	81·2	−2·44	−1·09	−0·81	+0·14	+3·28	+0·56	+0·36
Average volunteers	78·16	−2·3	−1·5	−0·94	−0·28	+2·53	+2·42	−0·06
Average patients ..	56·81	−3·99	−2·31	−1·1	+0·1	+2·32	+0·25	−0·2

volunteers continued to lose weight until the free intake of food and water was resumed, but the other gained a little weight on the 4th day on an intake of 1440 ml. of water. In the figure the weight loss is shown of Benedict's (1915) subject Levanzin who was allowed to consume 720 ml. of distilled water on the 1st day and 750 ml. on each of the 2nd, 3rd, and 4th days of his fast.

Discussion

In this investigation the response to starvation for water and food was not the same as that observed when such starvation was combined with the injury inflicted by a major operation. After operation renal conservation of sodium began earlier and was greater. In starvation the excretion of potassium in the urine did not increase as it did after a major abdominal operation but continued at about the same rate as before starvation began. During the 4 days of starvation the output of sodium was greater, and the output of potassium was smaller, than after operation combined with a similar degree of starvation. Although the loss of water as urine was very similar during starvation and when starvation and operation were combined, the source of the water was probably different. Judging by the quantities of endogenous sodium and potassium excreted in the urine, water was lost chiefly from the extracellular fluid during starvation alone but chiefly from the intracellular fluid when similar starvation was combined with operation. The large increase in urinary nitrogen excretion which characteristically follows injury combined with starvation (Cuthbertson 1936, Wilkinson et al. 1949) did not occur in these starved uninjured volunteers.



Daily change in weight. The average of 4 control patients, of 15 patients after various gastric operations, and of Benedict's Levanzin are plotted as percentages of the initial weight.

The weight losses have been expressed both for volunteers and patients as a percentage of the initial weight at the beginning of the experiment or at the end of operation. The average loss of the volunteers was 5·02% of 78·16 kg. (or 3·92 kg.) and of the patients was 6·36% of 56·81 kg. (or 3·61 kg.) If, because of the difference in the average weights of the volunteers and patients, the total losses are compared on the basis of the so-called typical adult male weighing 70 kg., the total average weight loss becomes 3·5 kg. for the volunteers and 4·4 kg. for the patients. The differences between volunteers and patients in the rate and duration of the loss of weight during the first 4 days suggest that some factor other than the simple deprivation of water and food is concerned in the large average loss of weight after operation. The failure of the patients to regain weight as rapidly after the 4th day as the controls did may be associated with the effects on gastric capacity of a radical gastrectomy.

From time to time it has been suggested that the greater part of the metabolic disturbance which follows sufficiently severe injury in well enough nourished subjects (and is indicated by changes in the composition of the urine) is due to starvation and not specifically to the injury. The observations now reported are in accord with classical reports that starvation alone causes only a small increase in urinary nitrogen excretion, no increase in potassium excretion, and a slow reduction in sodium excretion; when, in similar circumstances of environmental temperature and humidity, and bodily activity, starvation and operation are combined, there is a large increase in nitrogen excretion within 48 hours and of potassium excretion within 24 hours, and sodium excretion is much reduced.

Most of the weight loss by the volunteers is due to water loss in the urine and insensibly through the skin and in the expired air. The larger weight losses of the patients may be accounted for by their larger protein catabolism as indicated by the greater urinary excretion of nitrogen and potassium. The evidence obtained by the study of these volunteers and previously of patients after various gastric operations suggests that after major gastric operations there is a loss of body tissue which depends on the infliction of a severe surgical injury and is additional to the effects of starvation. It seems unlikely that this response to injury can be readily modified except by the prevention of starvation for water and food, and it is uncertain how far this can be profitably achieved in the biological sense by parenteral as opposed to oral feeding. Modification of the portion of the response which can be attributed to the infliction of injury would require interference with the normal whole-body response to injury, the nature of which is still imperfectly understood and the disturbance of which might do more to hinder healing than good in the prevention of tissue catabolism.

I am indebted to the four volunteers who submitted to this experiment for their cooperation, and to Miss Edna Simpson for technical assistance with the analyses.

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"The essential function of the city is bringing people together, to make communication and spiritual and emotional communion possible between large groups of people.... That once necessitated people living within a very close area and putting up with a great deal of congestion . . . because the means of communication have radically altered . . . the big city as a place of physical congregation has become an obsolete form. . . . We must now conceive of the essential elements of the city being available over a much wider area. None of the original services, none of the great cultural attributes of the city, will be lost because of this. On the contrary they will be performed under much better conditions than we are able to perform them now in our overcrowded centre."—LEWIS MUMFORD, *Listener*, Sept. 28, 1961, p. 463.

RISK OF PARENTS WHO HAVE HAD ONE CHILD WITH DOWN'S SYNDROME (MONGOLISM) HAVING ANOTHER CHILD SIMILARLY AFFECTED

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THREE questions are very important for genetic counselling in relation to Down's syndrome.

First, if parents have had one child with the syndrome, is there an increased risk of their having a second child similarly affected, and is the increase dependent on maternal age?

Secondly, if the answer is Yes, is the increase limited to a minority of the parents?

Thirdly, if the answer is again Yes, can these parents be identified cytologically?

This paper provides an answer to the first question, presenting data which show that there is a significantly increased risk of a second affected child, particularly for young mothers. Hamerton et al. (1961) provide partial answers to the second and third questions.

Theoretical Considerations

There are several pitfalls in assessing the chances that the sibs of index patients with a particular disorder will be affected by the same disorder. Some workers have based an estimate on the sibs born after the first affected person in the sibship, irrespective of, or without knowing, whether this was an index patient.* This will tend to give too high an estimate of the risks, as in Böök and Reed's (1950) estimate based on an early series, which Penrose (1934) had used for a study of maternal age and birth order. Another source of error, where ascertainment is incomplete, is to make no allowance for the greater probability that a sibship with two affected persons will come to notice. This omission will also tend to give too high an estimate of the risk.

*The index patient is that through whom a family is ascertained; a family may contain two or more index patients, provided that each came to notice independently.

In general, the best estimate is given by the ratio of affected sibs to total sibs of the index patients, excluding the index patient. Due allowance must be made for any effect of maternal age, or birth order, on the incidence of the condition; with Down's syndrome it is maternal age and not birth order which is important (Penrose 1934, Smith and Record 1955). Often a better estimate of the risk to sibs is given by the proportion affected of the younger sibs than of the older sibs of the index patient. For example, where there is a tendency to miss the diagnosis until a second affected child is born, the sibs born after the index patient will, provided that the condition is homogeneous, give a correct estimate of the risk; those born earlier will give too high an estimate because often the index patient would not have come to notice but for an older affected sib. A practical reason for preferring estimates based on younger sibs is that the diagnosis in them is likely to be more complete, since the parents and family doctor have been alerted.

Earlier Data

In 1934 L. S. Penrose listed 217 families containing a child with Down's syndrome. In 6 of these there were 2 sibs affected, and in one a pair of like-sex twins. But in 4 of the 6 the second affected child was born when the mother was at least 40 years old; and in 1949 Penrose wrote of Down's syndrome: "with such a common defect it is difficult to produce convincing evidence that the familial cases are due to familial concentration and not to chance sampling."

This was unfortunately still the case after Øster (1953, 1956) had conducted his thorough survey of 526 living patients with Down's syndrome in Denmark. Øster (1956) found 4 affected children in 343 sibs born after his index patients, and 3 affected in 1463 sibs born before his index patients. Taking the prevalence of Down's syndrome in Denmark as 1 in 618 live births, he estimated that the expected number of affected among the later sibs was 1·4, compared with the observed number of 4; and among the earlier sibs the expected number was 2·1, compared with an observed number of 3. One sibship contained 2 index cases, and so provided both an earlier and a later affected sib. Øster rightly concluded that his figures did not prove that there was any real increase over the random risk of a second affected child. The increase of the observed over the expected number of sibs with Down's syndrome did not reach the 5% level of significance (Poisson test). Øster's findings are summarised in table I.

TABLE I—PREVALENCE OF DOWN'S SYNDROME AMONG SIBS OF INDEX PATIENTS IN DENMARK (ØSTER 1956)

	Maternal age (yr.) at birth of sib						Total
	15–19	20–24	25–29	30–34	35–39	40–44	45+	
Later-born sibs:	..	26	65	75	96	70	11	343
Affected	..	1	1	2	..	..	..	4
Expected no. affected	..	0·018	0·045	0·085	0·344	0·721	0·196	1·409
Earlier-born sibs:	51	301	505	369	205	32	..	1463
Affected	..	1	1	1	..	..	..	3
Expected no. affected	0·031	0·208	0·353	0·421	0·734	0·330	..	2·076

TABLE II—SIBS BORN AFTER INDEX PATIENT CLASSIFIED BY MATERNAL AGE (THOSE WITH DOWN'S SYNDROME SHOWN IN PARENTHESES)

—	Age of mother (yr.) at birth of younger sib														Total		Grand total	Expected no. of affected sibs	
	15–19		20–24		25–29		30–34		35–39		40–44		45+					A	B
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F			
Age (yr.) of mother at birth of index patient. 15–19	1	1	4	9	4	2	..	..	..	..	..	..	..	..	9	12	21	0·006	0·013
20–24			(1)		(1)	(2)									(2)	(2)	(4)		
	..	..	9	9	29	29	4	7	1	..	1	..	..	..	44	45	89	0·059	0·082
25–29	..	..	..	..	12	14	23	24	10	9	1	2	..	..	46	49	95	0·198	0·182
30–34											(1)				(1)		(1)		
	..	..	..	..	..	1	9	7	23	11	6	6	..	..	38	25	63	0·318	0·280
35–39	..	..	..	..	..	..	..	..	6	13	11	7	..	..	17	20	37	0·322	0·266
40–44	..	..	..	..	..	..	..	..	..	..	1	5	..	1	1	6	7	0·111	0·083
Total			(1)		(1)	(2)					(1)				(3)	(2)			
	1	1	13	18	45	46	36	38	40	33	20	20	..	1	155	157		..	..
Grand total	2		(1) 31		(3) 91		74		73		(1) 40		1				(5) 312	..	..
Expected no. of affected sibs:																			
A	0·000		0·009		0·026		0·127		0·257		0·567		0·026				1·012	..	..
B	0·001		0·020		0·067		0·091		0·279		0·429		0·019				0·906	..	..

TABLE III—SIBS BORN BEFORE INDEX PATIENTS CLASSIFIED BY MATERNAL AGE (THOSE WITH DOWN'S SYNDROME SHOWN IN PARENTHESES)

		Age of mother (yr.) at birth of older sib														Total		Grand total	Expected no. of affected sibs	
		15–19		20–24		25–29		30–34		35–39		40–44		45+						
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F		A	B
Age (yr.) of mother at birth of index patient:	15–19	..	1	..	..	..	..	..	..	..	..	..	..	..		..	1	1	0·000	0·001
	20–24	3	4	4	8	..	..	..	..	..	..	..	..	..	..	7	12	19	0·003	0·012
	25–29	1	4	16	26	9	9	..	..	..	..	..	..	..	..	26	39	65	0·017	0·042
	30–34	1	..	(1) 12	14	29	(1) 34	13	15	..	..	..	..	..	..	(1) 55	(1) 63	(2) 118	0·073	0·098
	35–39	1	3	22	23	46	54	56	53	19	(1) 14	..	..	..	..	144	(1) 147	(1) 291	0·345	0·364
	40–44	2	1	25	34	66	50	40	62	42	47	6	10	..	..	181	204	385	0·765	0·762
	45+	2	..	4	1	2	5	5	7	5	9	3	4	..	(1) 1	21	(1) 27	(1) 48	0·198	0·171
Total		10	13	(1) 83	106	152	(1) 152	114	137	66	(1) 70	9	14	..	(1) 1	(1) 434	(3) 493	..	..	..
Grand total		23		(1) 189		(1) 304		251		(1) 136		23		(1) 1				(4) 927	..	..
Expected no. of affected sibs:																				
A		0·000		0·053		0·088		0·432		0·479		0·326		0·026				1·404	..	..
B		0·012		0·119		0·225		0·309		0·520		0·247		0·019				1·451	..	..

Material

There were 725 patients with Down's syndrome who attended The Hospital for Sick Children between 1944 and 1955 and who, at the time of referral, were domiciled in London, the Home Counties, or the adjoining counties. We have followed the fate of 698 of these patients (Carter 1958) and collected family data, on visits to the homes of the patients, of 642 of them. It so happened that no family included more than 1 index patient; therefore the data given below refer to 642 families. The incomplete information available on the families of the other 56, whose parents could not be traced or did not wish to cooperate, indicate that they do not differ essentially from the main group.

TABLE IV—ESTIMATE OF PREVALENCE OF DOWN'S SYNDROME IN 5-YEAR MATERNAL AGE-GROUPS, FROM DISTRIBUTION OF MATERNAL AGE AT BIRTH OF INDEX PATIENTS AND OF ALL BIRTHS IN ENGLAND AND WALES FOR THE CORRESPONDING YEARS

	Maternal age (yr.)							
	15–19	20–24	25–29	30–34	35–39	40–44	45+	Total
Numbers:								
Mothers of index patients ..	7	65	91	107	191	161	20	642
General population ..	21·19	169·30	201·36	142·33	81·58	24·48	1·75	642
Down's syndrome per 1000 births	0·54	0·63	0·74	1·23	3·82	10·72	18·63	..

The total number of live-born later sibs, and the patients with Down's syndrome included among them, are shown in table II. They are classified by maternal age at the birth of the index patient and at the birth of the subsequent sib. The same data for the older sibs are shown in table III.

Two estimates are shown for the expected number of affected among the sibs. Estimate A is based on a direct study of the prevalence of the condition among births at maternity hospitals (Carter and MacCarthy 1951). Estimate B is calculated indirectly by comparing the maternal age for each of the 642 index patients in the series with the maternal-age distribution for England and Wales for the same year. The comparison is shown in table IV, together with the prevalence of Down's syndrome estimated on this basis, assuming the overall prevalence in the survey area to be 1·62 per 1000 maternities (Carter and MacCarthy 1951)—that is about 1·63 per 1000 live births.

All the younger sibs have been personally seen (C. O. C.) except for a few who died young. For these exceptions records from the hospital where the child died were obtained for all except 1, who died at home and for whom only the death certificate was available. The causes of the deaths in infancy among the younger sibs are shown in table V.

No special effort was made to examine all the surviving older sibs of index patients. It was thought unlikely that a diagnosis of Down's syndrome would have been missed in the survivors; but once again the causes of infant deaths were documented. If the sibs with Down's syndrome are excluded, the infant death-rates—6 in 312 live-born younger sibs and 28 in 927 live-born older sibs—are similar to those in the general population. Possibly one or two of the sibs who died in infancy, particularly among the older sibs, were undiagnosed cases of Down's syndrome; but such failures of diagnosis among infant deaths will also lead to an under-estimate of the prevalence in the general population.

Besides the live births, there were 6 stillbirths occurring after, and 32 before, the birth of the index patient. In none of these stillbirths was Down's syndrome diagnosed, though it was suspected in 1 born after the index patient. There were 58 miscarriages after, and 146 before, the birth of the index patients. Neither the stillbirth-rate nor the miscarriage-rate differ significantly from that in the general population.

The twins of the index patients form a special group. Unless the chromosome mutation occurs after zygote formation, the monozygotic twin of an index patient with Down's syndrome will always be similarly affected, and there is no convincing exception to this rule. In the

TABLE V—INFANT MORTALITY AMONG YOUNGER SIBS OF INDEX PATIENTS

Sex	Age at death	Cause of death
F	32 hr.	Atelectasis
M	5 days	Intracranial hæmorrhage
M	3 days	• Bronchopneumonia
M	5 mos.	† Pulmonary collapse, congenital heart malformation, Down's syndrome
F	4 days	Bronchopneumonia, congenital heart malformation, Down's syndrome
F	1 day	Premature, atelectasis
F	11 weeks	Congenital heart malformation, bilateral congenital hydronephrosis, Down's syndrome
M	5 mos.	Congenital heart malformation, Down's syndrome
M	4 hr.	Atelectasis
M	4 weeks	Marasmus, gastroenteritis, Down's syndrome
F	5 weeks	‡ Bronchopneumonia, hydronephrosis

• Death certificate only; no hospital report.
† Appearance noted in maternity hospital to be suggestive of Down's syndrome, and family warned that child would be mentally backward, but diagnosis not fully documented.
‡ Additional diagnosis of Down's syndrome made by pathologist, but pædiatrician disagreed and clinical photograph does not suggest Down's syndrome.

TABLE VI—TWINS OF INDEX PATIENTS

Unlike sex pairs	Like sex pairs known to be dizygotic	Like sex pairs, type of twinning undetermined
•*F* M†	•*M* M	•‡*F* F
•*F* M	•*M* M	•*M* M†
•*F* M	•*F* F	•§*F* F
•*M* F	•*M* M	•*F* ‖*F*
•*M* F	•*M* M	..

• = index patient. *F* or *M* = Down's syndrome. † = stillborn.
‡ = died at 4 months. § = died at 15 months. ‖ = died at 7 months.

TABLE VII—RELATIVE PREVALENCE OF DOWN'S SYNDROME IN SIBS OF INDEX PATIENTS AND IN GENERAL POPULATION: PRESENT SERIES AND ØSTER'S SERIES COMBINED

	Maternal age (yr.) at birth of sib				
	15–24	25–29	30–34	35+	Total
Younger sibs affected: ..	2	4	2	1	9
Expected number affected	0·039	0·112	0·176	1·988	2·315
Observed/expected ..	51·3	35·7	11·4	0·5	3·9
Older sibs affected: ..	2	2	1	2	7
Expected number affected	0·370	0·578	0·730	1·850	3·527
Observed/expected ..	5·4	3·5	1·4	1·1	2·0

present series there were 14 twins of index patients, and the information on them is summarised in table VI. Unless otherwise stated in the table, the twin is alive and well. In 4 instances of like-sex twins, the index patient or the twin died before the type of twinning was established.

Discussion

Considering first the younger sibs of index patients, who probably provide the best estimate of the risks of a second mongol child, the 5 affected sibs observed are significantly more, at the 1% level (Poisson test), than the higher estimate of the number expected—1·4. There are, however, several possible sources of error in this comparison. For example, the estimates of the prevalence of Down's syndrome in the general population may be too low, though based on maternity hospitals in which all infants are carefully examined. Also there is some doubt of the correct diagnosis in 2 of the subsequent sibs, as indicated in the footnotes to table IV; in 1 of these children the diagnosis of Down's syndrome was accepted, in the other it was not. But, taken together with the very similar findings in Øster's (1956) Danish series, there is little doubt that there is a significant increase in the risk of a second affected child. In the two series together there are 9 affected sibs, when under 3 would be expected.

In analysing further the ratio of the number of affected sibs observed with that expected, the ratio can be related either to mother's age at the birth of the sib or to her age at the birth of the index patient. The recent discovery that the genetic basis for Down's syndrome is not entirely uniform, as well as studies of maternal age in familial Down's syndrome (Penrose 1951), suggest that the latter comparison is more meaningful. For an analysis by maternal age at the birth of the sib the Danish series can be combined with the present one. Using estimate B, the lowest row of figures in tables II and III, the combined comparison is summarised in table VII.

In the younger sibs the ratio of observed to expected affected children falls from the high figure of 50 for mothers under 25 years of age to unity or less for mothers over 35 years. With the older sibs the ratios are much lower, falling from 5 to unity with increasing maternal age. This difference suggests that what essentially determines the ratio is mother's age at the birth of the index patient, not of the sib.

The ratio of observed to expected affected sibs according to mother's age at the birth of the index patient, using estimates A and B in the right-hand columns of tables II and III, is shown in table VIII, for the present series. This information is not given for the Danish series. There is a 30–60 fold increase in the risk of a second affected child for mothers who had the index patient when they were under the age of 25, a smaller increase for mothers between the ages of 25 and 34, and little or no increase for mothers who had the index patient at the age of 35 or over.

This finding is at least partially explained by the recent discoveries of occasional instances where one or other parent of a child with Down's syndrome has a chromosome abnormality. The cytological examination of the families in this series with 2 sibs affected is described by Hamerton et al. (1961). In three of the four instances where a mother had an index patient when she was under the age of 25 and had a second affected child, one or other parent had a chromosome abnormality.

From the practical viewpoint of genetic counselling, where chromosome studies are not available, the present findings and Øster's Danish survey suggest that parents who have had one child with Down's syndrome, and

TABLE VIII—COMPARISON OF OBSERVED AND EXPECTED NUMBER OF AFFECTED SIBS ACCORDING TO MOTHER'S AGE AT BIRTH OF INDEX PATIENT

	Maternal age (yr.)			
	15–24	25–35	35+	Total
Observed affected sibs ..	4	3	2	9
Expected affected sibs:				
A	0·068	0·606	1·741	2·415
B	0·108	0·602	1·646	2·356
Observed/expected:				
A	58·8	5·0	1·1	3·7
B	37·0	5·0	1·2	3·8

have no other close relative affected, may be told that the risk is of the order of 1–2% irrespective of maternal age. But for young mothers at least, chromosome studies are a most valuable aid to genetic counselling.

Summary

Data are presented on the sibs of 642 index patients with Down's syndrome.

Of 312 sibs born after the index patient 5 also had Down's syndrome, whereas only 1 would have been expected from the prevalence in the general population. Of 927 earlier sibs 4 were affected, whereas about 1·5 would have been expected.

The ratio of the number of sibs found affected to the number expected is much influenced by the age of mothers at the birth of the index patient. For mothers under 25 years the risks are something like 50-fold the random risk, and for mothers of 25–34 years 5-fold the random risk, whereas no increase is apparent for mothers over the age of 35.

In part at least the explanation of these findings is that some young mothers of children with Down's syndrome, but rarely older mothers, will have a high risk of a second affected child because either they or their husbands have a chromosome abnormality.

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References overleaf

CHROMOSOME STUDIES IN DETECTION OF PARENTS WITH HIGH RISK OF SECOND CHILD WITH DOWN'S SYNDROME

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IT is important to know whether the increase in the risk of a second child with Down's syndrome is due to the small minority of parents of such children who themselves have a chromosome anomaly. To provide at least a partial answer to this question, chromosome studies were made on the families of the 9 index patients who had an affected sib, from a series of 642 at The Hospital for Sick Children (Carter and Evans 1961).

Peripheral-blood cultures (Moorhead et al. 1960) were established from the index patients (if still alive), both parents, and, where appropriate, the grandparents and sibs. In the case of one family where mosaicism was found, skin cultures from the index patient and his father were also examined. A summary and analysis of the chromosome counts in the nine families are given in table I.

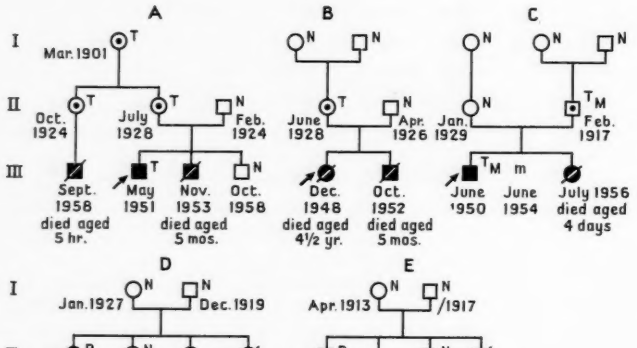

Fig. 1—Pedigrees of five mongol index patients with a younger mongol sib.

↗ = index patient
■ = mongol
⊙ = carrier
R = trisomy 21
T = translocation
M = mosaicism
N = normal karyotype
Numerals represent month and year of birth.

Results

FIVE FAMILIES WITH INDEX PATIENT AND AFFECTED YOUNGER SIB

Three families in this group showed evidence of Down's syndrome due to chromosome translocation and the carrier state in one or other of the parents.

First Family (fig. 1, A)

The pedigree and chromosome findings in the family with the most striking concentration of affected individuals have already been published (Carter et al. 1960). The affected index patient had 46 chromosomes and carried a 15/21 translocation. He was born when his mother was 22 and he had two younger sibs, one affected, born when the mother was 25, and one normal. The mother, a sister of the mother (who had also had an affected boy), and the mother's mother were all carriers of the translocation, and had only 45 chromosomes, whilst the father and other sib were chromosomally normal.

Second Family (fig. 1, B)

The mother in this family had given birth to the index patient at the age of 20, and to the affected sib at the age of 24. The index patient and her affected sib both died of congenital heart-disease at the ages of 5 years and 5 months respectively. The mother had 45 chromosomes, an apparent 21/21 or 21/22 translocation, only 2 chromosomes remaining in the 21–22 group, and 5 resembling the 19–20 group. Her karyotype is shown in fig. 2. The chromosomes of both her parents were examined but neither was found to carry the translocation.

Third Family (fig. 1, C)

The mother had given birth to the index patient at the age of 21 and the affected sib at the age of 27. The index patient is still alive, and the affected sib died of congenital heart-disease at the age of 4 days. Analysis of the chromosomes in this family revealed a situation very similar to that in the family reported by Fraccaro et al. (1960). Chromosome-counts from peripheral-blood cultures of the index patient showed that the majority of cells had 46 chromosomes, whilst a few had 47. Analysis of cells from the 46-chromosome clone (fig. 3) revealed 5 chromosomes morphologically resembling chromosomes of the 19–20 group and only 3 chromosomes in the 21–22 group. The cells with 47 chromosomes (fig. 4) were analysed as follows: there were 5 chromosomes in the 19–20 group and 4 in the 21–22 group. Cells from the skin-cultures kindly carried out by Dr. M. Fraccaro on the index patient showed only 46 chromosomes with an analysis identical to the 46-chromosome clone in the leucocyte culture.

Two clones of cells were also found in the leucocyte cultures of the father. The first and predominant one had 46 chromosomes, and the karyotype analysis was that of a normal male. The second and smaller clone had 47 chromosomes and an identical analysis to the 47-chromosome clone in the index patient (fig. 4). Skin-cultures from the father revealed only normal male cells.

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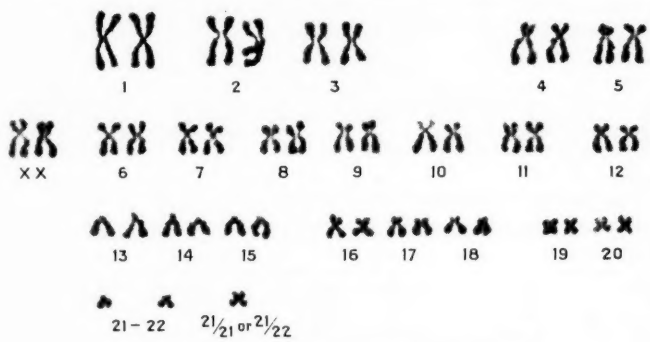

Fig. 2—Karyotype of mother in second family.

Whilst other interpretations are possible, it seems probable that both the father and son are chromosome mosaics. The additional chromosome resembling one of the 19–20 group in all cells of the index patient and in the abnormal cells of the father is thought to be an isochromosome for the long arm of chromosome 21. If this is correct, then the index patient is in effect predominantly trisomic for chromosome number 21, whilst a few cells are tetrasomic, and his father's cells have predominantly normal chromosomes with a few tetrasomic cells.

The situation in the family reported by Fraccaro et al. (1960) can also be attributed to mosaicism. In this case the affected boy was found on skin-culture to carry an isochromosome and as a result to be in effect trisomic for chromosome number 21, whilst on skin-culture his father was in effect tetrasomic for that chromosome. There was no mosaicism in the skin-culture, but recently M. Fraccaro and J. Lindsten (personal communication) have found that counts obtained from leucocyte-cultures of the father have only 46 chromosomes and a normal male karyotype. It is presumed that the normality of this man and of the father in the family we report is due to the possession of a substantial number of normal cells. These observations are discussed in greater detail elsewhere (Hamerton 1961).

Fourth and Fifth Families

The pedigrees of the remaining two families are shown in fig. 1, D and E. In each case the chromosomes of the index patients showed regular trisomic 21 Down's syndrome, and the parents had normal karyotypes. The

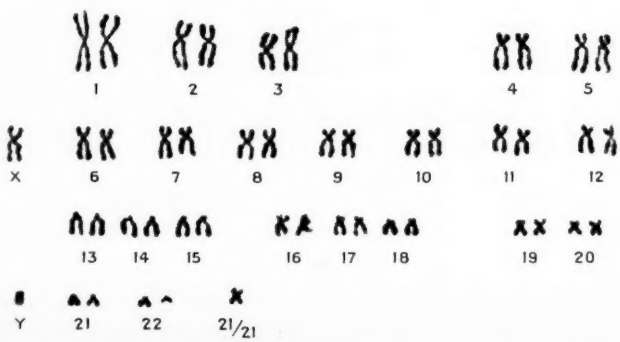

Fig. 4—Karyotype of cells with 47 chromosomes of index patient in third family.

maternal ages at the births of the index patient and of the affected younger sib were 20 and 27 in one family and 33 and 43 in the other.

FOUR FAMILIES WITH INDEX PATIENT AND AFFECTED OLDER SIB

The four families in this group showed no evidence of translocation Down's syndrome and the parents in each family had normal karyotypes. In three the index patient was shown to be a " regular " trisomic 21 case of Down's syndrome. In the fourth the index patient was dead, but his affected older sib was found to be a " regular " trisomic 21 patient (L. S. Penrose, personal communication). The pedigrees are shown in fig. 5. The maternal ages at the births of the index patients and their affected older sibs were 38 and 27; 47 and 45; 34 and 29; 33 and 20. These findings are summarised in tables II–IV. In tables II and III the sibs are tabulated according to maternal age at the birth of each sib, normal or affected. In table IV both groups of sibs—those born before and

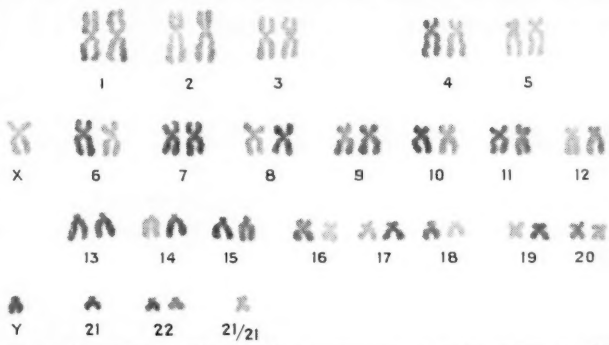

Fig. 3—Karyotype of cells with 46 chromosomes of index patient in third family.

those born after the index patient—are tabulated according to maternal age at the birth of the index patient. The expected numbers are calculated from the frequency of births of children with Down's syndrome at the different maternal ages in the series of Carter and MacCarthy (1951).

Discussion

Examination of the results obtained from the series of five families in which the second affected child was born after the index patient shows that, if chromosome analysis had been available at the time of the birth of the index patient, it would have been possible to warn the parents in three of the cases that they had a considerable risk of a second affected child. In only four of the nine families in the whole series with two affected sibs were both patients born before the mother was aged 30; and in three of these four families a chromosome anomaly involving chromosome number 21 was present in one or other parent. The value of chromosome studies in assessing the chances of a young mother having a second affected child is clear.

The findings, however, are not yet sufficient to answer the question whether parents of one " regularly " affected child, who have an

apparently normal chromosome constitution themselves, have no more than the random risk of a second affected child. In the series of children born after the index patient (table II) exclusion of the three families with a chromosome translocation or isochromosome involving number 21 still leaves two affected sibs where a little over one might be expected. Similarly, among the children born before the index patient (table III) there were four affected sibs when under two might have been expected. There are several possible sources of error in the calculation of the expected prevalences of Down's syndrome in the two groups of children, and neither difference between expected and observed incidence is significant at the 5% level; but the differences do suggest that there might still be an increase in the risk of a second affected child after the high-risk families detected by chromosome studies are excluded. If the findings are tabulated by maternal age at the birth, not of the sib, but of the index patient, as in table IV (and table VIII of Carter and Evans 1961), there are strong indications of a residual increase in the risk for maternal age under 35, but none above this age.

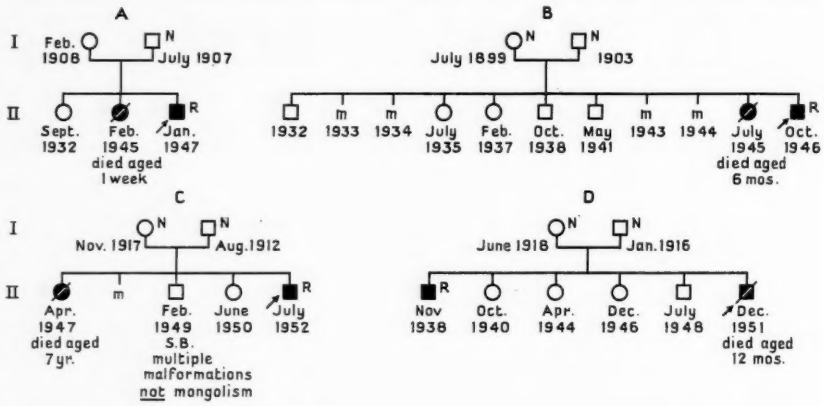

Fig. 5—Pedigrees of four mongol index patients with an older mongol sib (for key see fig. 1).

Assuming that there is a real increase at any rate for mothers who are still young when they bear an index

TABLE I—SUMMARY OF CYTOLOGICAL DATA AND CHROMOSOME-COUNTS IN FAMILIAL MONGOLS

Position in family	Pedigree designation	Chromosome counts <45	45	46	47	>47	Total cells	Diploid no.	Chromosome analysis
Family 1:									
Index patient	III: 2	3	..	*24*	3	..	30	46	15/21 translocation
Mother	II: 2	9	*27*	3	..	..	39	45	15/21 translocation
Brother	III: 4	17	6	*20*	..	..	43	46	Normal male
Grandmother	I: 1	3	*8*	..	..	..	11	45	15/21 translocation
Father	II: 3	..	..	*15*	..	..	15	46	Normal male
Maternal aunt	II: 1	8	*6*	..	..	..	14	45	15/21 translocation
Family 2:									
Mother	II: 1	5	*24*	1	..	..	30	45	21/22 translocation
Father	II: 2	5	4	*21*	..	..	30	46	Normal male
Grandfather	I: 2	2	5	*23*	..	..	30	46	Normal male
Grandmother	I: 1	6	4	*55*	3*	..	68	46	*2–47 additional X–6–12 group; 1–47 acentric fragment
Family 3:									
Index patient	III: 1	29	23	*128*	*5*	..	185	46/47	Trisomic/21 tetrasomic 21/mosaic
Father	II: 2	12	14	*100*	*4*	..	130	46/47	Normal/tetrasomic 21/mosaic
Mother	II: 1	4	6	*20*	..	..	30	46	Normal female
Grandmother	I: 2	2	4	*23*	1	..	30	46	Normal female
Grandfather	I: 3	2	5	*23*	..	..	30	46	Normal male
Maternal grandmother	I: 1	2	2	*26*	..	..	30	46	Normal female
Family 4:									
Index patient	II: 1	..	4	5	*21*	..	30	47	Regular mongol
Sister	II: 2	5	4	*21*	..	..	30	46	Normal female
Sister	II: 3	Culture failed							
Mother	I: 1	1	7	*23*	..	..	31	46	Normal female
Father	I: 2	10	2	*18*	2	..	32	46	Normal male
Family 5:									
Index patient	II: 1	3	2	4	*12*	..	21	47	Regular mongol
Brother	II: 3	2	6	*22*	..	..	30	46	Normal male
Mother	I: 1	2	6	*20*	2*	..	30	46	Normal female * acentric fragments
Father	I: 2	2	3	*8*	..	..	13	46	Normal male
Family 6:									
Index patient	II: 3	1	1	1	*27*	..	30	47	Regular mongol
Father	I: 2	2	1	*26*	1	..	330	46	Normal male
Mother	I: 1	Culture failed							
Family 7:									
Index patient	II:11	..	1	3	*25*	1*	30	47	Regular mongol * 6/21–22 group
Mother	I: 1	3	1	*22*	..	..	26	46	Normal female
Father	I: 2	2	2	*25*	1*	..	30	46	Normal male * additional X–6–12 group
Family 8:									
Index patient	II: 5	..	..	3	*27*	..	30	47	Regular mongol
Father	I: 2	3	4	*23*	..	..	30	46	Normal male
Mother	I: 1	1	1	*28*	..	..	30	46	Normal female
Family 9†									
Father	I: 2	..	1	*17*	..	..	18	46	Normal male
Mother	I: 1	4	6	*20*	..	..	30	46	Normal female

* Analysis of hyperdiploid cells. † Index patient regular mongol (L. S. Penrose, personal comunication).
Figures in italics indicate modal number.

TABLE II—CHILDREN BORN AFTER INDEX PATIENT

—	Maternal age (yr.) at birth of sib							Total
	15–19	20–24	25–29	30–34	35–39	40–44	45+	
Total children	2	31	91	74	73	40	1	312
Translocation Down's syndrome	..	1	2	..	..	..	..	3
Regular Down's syndrome	..	..	1	..	..	1	..	2
Expected Down's syndrome	0·000	0·009	0·026	0·127	0·257	0·567	0·026	1·012

TABLE III—CHILDREN BORN BEFORE INDEX PATIENT

—	Maternal age (yr.) at birth of sib							Total
	15–19	20–24	25–29	30–34	35–39	40–44	45+	
Total children	23	189	304	251	136	23	1	927
Regular Down's syndrome	..	1	1	..	1	..	1	4
Expected Down's syndrome	0·000	0·053	0·088	0·432	0·479	0·326	0·026	1·404

patient with regular trisomy for chromosome 21, two possible explanations occur to us. The first is that, in at least a small proportion of these families, there is a gene or genes which act to produce an increase in non-disjunction among the individuals carrying them. The second is that some of the parents who are phenotypically normal are themselves trisomic-21/normal mosaics. Clarke et al. (1961) have reported trisomy-21/normal mosaicism in an intelligent child with some features of Down's syndrome. They found only normal cells in leucocyte-cultures from peripheral blood, whilst both normal and trisomic cells were found in the skin-culture. With such mosaicism it is possible to envisage a phenotypically normal individual with normal intelligence and only a few tissues involved. If these tissues include the gonads, then the frequency of affected children will depend on the proportion of affected gametes. At the worst, with all the gonadal cells trisomic, equal numbers of normal and affected children might be expected.

Further analysis of the parents in the six families with two " regularly " affected children is being undertaken to investigate these points.

Summary

Chromosome studies have been made on the families of 9 index patients who had an affected sib in a series of 642 patients from The Hospital for Sick Children.

Of five families with an index patient and an affected younger sib, three were found to be carrying translocations or isochromosomes involving chromosome 21. In the remaining two families, and in four families with an index patient and an older affected sib, the parents were found to be normal and the affected children to have " regular " Down's syndrome with trisomy of chromosome 21.

TABLE IV—SIBS OF INDEX PATIENTS BY MATERNAL AGE AT THE BIRTH OF THE INDEX PATIENT

—	Maternal age (yr.) at birth of index patient			Total
	15–24	25–34	35+	
Total children	130	341	768	1239
Translocation Down's syndrome	3	..	..	3
Regular Down's syndrome ..	1	3	2	6
Expected Down's syndrome ..	0·068	0·606	1·741	2·415

In all three " translocation " families the mother was under the age of 25 at the birth of the index patient; and these families account for most, but probably not all, of the increased risk that young mothers of a child with Down's syndrome will have a second affected child.

Two possible explanations for an increase in the risk of a second child with " regular " Down's syndrome are an inherited predisposition to non-disjunction and the occurrence of trisomy-21/normal mosaicism in one or other parent.

We are indebted to the staff of The Hospital for Sick Children for access to their patients; to Prof. Paul E. Polani and Dr. J. A. Fraser Roberts for reading the manuscript; to Miss V. M. MacGuire, Miss Anne Horsley, and Miss Susan Brennels for valuable technical assistance; and to Mrs. K. A. Evans for help with the families of the index patients.

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URINARY ŒSTROGEN MEASUREMENTS AFTER OOPHORECTOMY AND ADRENALECTOMY FOR ADVANCED BREAST CANCER

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THE steps by which endocrine measures were introduced in the treatment of advanced breast cancer are now well known and have been reviewed elsewhere (Huggins 1954). There is now abundant evidence that oophorectomy and adrenalectomy or hypophysectomy will cause a temporary regression in the disease in some patients (Lipsett et al. 1957, Pearson and Ray 1959, Luft et al. 1958). There is some evidence that hypophysectomy, adequately done, is slightly superior to adrenalectomy (Atkins et al. 1957, Pearson and Ray 1959). Unfortunately, however, less than 50% of these patients obtain a remission by such measures—and this has led to the advocacy of oophorectomy together with cortisone or prednisone to suppress corticotrophin (A.C.T.H.) production in the hope of obtaining an equal remission, and some authors believe that this can be achieved. (Lemon 1959, Brinkley and Pillers 1960, Persson and Risholm 1960).

Another approach has been to find means of selecting for ablative endocrine surgery only those patients who will respond. Huggins and Dao (1952) thought that the histological characteristics of the tumour might be helpful in selection but few have been able to confirm this. The effect of provocative doses of stilbœstrol on urinary calcium excretion has been thought useful in patients with bony metastases (Emerson and Jessiman 1956) but not all authors have found this and not all patients have bony metastases.

Since those who responded to endocrine surgery were believed to have tumours which were hormone dependent, it was natural that a study of the hormonal background of these tumours, before and after endocrine surgery, should be undertaken. By such means it was hoped to find prognostic criteria helpful in selecting patients whose tumours would regress, and the hormonal changes associated with this response might give fundamental information on the disease itself.

In a study from Edinburgh, Strong et al. (1956) were able to measure the excretion of three œstrogens, pregnanediol, 17-ketosteroids, and pituitary gonadotrophins in thirteen patients undergoing bilateral adrenalectomy and oophorectomy for mammary cancer. The pattern of hormone excretion in patients who responded favourably to the operations did not differ from that in patients who showed no improvement. These authors also drew attention to the fact that significant quantities of œstrogens might be excreted after adrenalectomy which made the rigid division of tumours into œstrogen dependent and independent types, depending on surgical response, less certain. This finding of œstrogen excretion after adrenalectomy was confirmed by Bulbrook et al. (1958a and b). Postoperative œstrogen excretion did not exclude objective regression, and progression of the disease might take place in spite of the fact that no œstrogen could be detected in the urine. They found, however, that those patients who responded to surgical hypophysectomy had lower postoperative values than those who failed to benefit. On the other hand, the response achieved by destruction of the pituitary with yttrium implantation was not found to be related to the levels of œstrone, œstradiol, and œstriol in the urine postoperatively nor were the preoperative levels of these hormones in any way correlated with response (McAllister et al. 1960). Since prolactin and growth hormone are known to affect breast development the levels of these hormones might also be of great significance in such patients but sufficiently accurate methods of assay have not been available for use. The demonstration of mammotrophin activity in the urine of patients with breast cancer using hypophysectomised weanling mice has been developed by Hadfield (1958), but there is no agreement on what this activity measures (Loraine 1958) and others have had difficulty with this method (Williams 1958).

Analysis of androgen excretion has also been used. Allen et al. (1957) found the ratio of urinary 11—deoxy to the 11—oxy 17-oxosteroids was of prognostic value. In those patients who benefited from operation the ratio was greater than 1 and the excretion pattern approximated to that found in healthy subjects. In those who did not benefit the ratio was less than 1 and the excretion pattern closely resembled that found after operation and this finding applied to patients undergoing either hypophysectomy or adrenalectomy. Recently from the same group it has been suggested that the response to hypophysectomy, and to a less extent adrenalectomy, can be predicted by measurement of the urinary levels of 17-hydroxy-corticosterone and ætiocholanolone (Bulbrook et al. 1960). These authors found the mean 17-hydroxycorticosterone value higher and the mean ætiocholanolone value lower in those failing to respond. Hobkirk et al. (1959) failed to find assays of the fractionated 17-oxosteroids of use for predicting the response to pituitary irradiation but, as has been noted earlier, the effect of irradiation on œstrogen excretion apparently differs from that of surgical ablation.

In summary, then, it might be true to say that hormone studies on these patients have given inconclusive and perhaps surprising results. On the one hand, androgen studies have in some hands, though not in others, proved of value in selecting those likely to respond to endocrine surgery, while almost all workers have found the preoperative urinary excretion of œstrone, œstriol, and œstradiol unhelpful and the changes produced in their output unrelated to response. This does not necessarily mean that œstrogens are unimportant. Firstly, œstrogens are known which have not yet been measured in these patients. Secondly, the methods of measuring urinary œstrogens may not have been fine enough to measure the changes involved. Lastly, the urinary excretion of œstrogens may be a poor indicator of metabolism at a cellular level. In this paper the second of these possibilities is considered by using a method of measuring urinary œstrogens considerably more sensitive than those usually used. In the paper which follows, the response to endocrine surgery is related to uptake of tritated hexœstrol by the tumour cells.

The Patients

This report is based on a study of fifty-four patients. Forty-nine within 5 years of their menopause underwent bilateral adrenalectomy with the addition of oophorectomy, and in the remaining five premenopausal patients oophorectomy was done in the first instance.

Of these, eleven had presented with advanced carcinoma of breast without previous surgery. The remainder presented with evidence of local recurrence or distant metastases after previous simple or radical mastectomy and radiotherapy for the primary lesion.

Nine patients had undergone a period of testosterone therapy, five with some improvement. Of two patients receiving prolonged stilbœstrol therapy one showed a temporary objective remission.

Of these fifty-four patients, twelve were premenopausal. Of the remaining forty-two postmenopausal patients twelve were within 5 years of their menopause at the time of endocrine surgery.

The patients' ages ranged from 39 to 68 years, the mean age being 50·4.

The time elapsing between a histological diagnosis of breast carcinoma and endocrine surgery ranged from a few weeks to 9·5 years, the mean period being 52 months.

Selection of Cases

On the whole, patients over 65 years of age were not readily accepted as suitable for surgery. Although hepatic metastases did not exclude the possibility of surgery, the presence of jaundice was considered an absolute contraindication. In this initial series patients with cerebral metastases were not excluded. Most cases had either very extensive local disease or multiple distant metastases. Where local disease or single regional metastases could be treated by radiotherapy, this was regarded as the treatment of choice in the first instance and such patients underwent endocrine surgery only if progression continued in spite of radiotherapy.

Preoperative Assessment

Before operation all patients had accurate measurement of the breast tumour if present as well as any skin metastases. X-rays of any chest or bony metastases were taken under known standard conditions and further radiological screening of skull, chest, spine, and pelvis was done in all patients regardless of symptoms. Liver enlargement and any palpable abdominal metastases were carefully noted and measured.

Any patient with abnormal neurological signs had electroencephalography recordings in addition to clinical assessment.

Estimation of Œstrogens in Urine

Urines were collected for three consecutive days before operation. If the woman was premenopausal the collection was arranged about the 20th day of the menstrual cycle if possible. After operation three consecutive 24-hour specimens were again collected at intervals.

Each 24-hour specimen was collected into a jar containing 5 ml. 50% H_2SO_4 (v/v). The œstrogens in a specimen collected in this way will remain stable at room temperature for about two weeks. If it was found impossible to process the urines within this time they were stored in the deep freeze.

The urines were measured and one-third of each day's urine bulked together. This gave a specimen equivalent to one day's output of urine in which the œstrogen concentration was equal to the mean of three days' œstrogen excretion.

This urine was then hydrolysed, extracted, chromatographed on a Celite column, and estimated fluorimetrically, according to the method of Preedy and Aitken (1961).

The extraction procedure used in this method was that of Engel et al. (1950). 85 vols. of urine were refluxed for 45 minutes with 15 vols. concentrated HCl and then cooled in tap water. When cool it was extracted four times with ether. The ether was washed with saturated $NaHCO_3$ and then with water and evaporated to dryness. The residue was taken up in toluene and extracted with NaOH. The combined NaOH extracts were washed twice with *n*-hexane. The pH was then adjusted to 9·5 with 12*N* H_2SO_4 and, when cool, again extracted with ether. The combined ether extracts were washed with water and dried. This extract was now ready to be chromatographed. As the œstrogen levels in patients who have been adrenalectomised and oophorectomised are extremely low, double chromatography was used.

Celite was mixed with the stationary phase in the proportions three parts Celite, by weight, to two parts stationary phase, by volume, and the columns were packed according to the procedure of Martin (1951) and Morris and Williams (1953). The first column used was 1·2 cm. in diameter and the Celite was packed to a depth of 10 cm. Some dry Celite was packed on top of this column and the extract from 50% of one day's output of urine dissolved in 0·25 ml. 72% methanol, which was the stationary phase, applied to the top of this dry Celite. When this had been absorbed a little more dry Celite was packed on top and the remainder of the column filled with the first mobile phase. This large column was then attached to a syphon calibrated to delivery 4·0 ml. and the whole fitted to a fraction collector. A phase changer filled with the mobile phases was fitted on top of the column and the dead space between the top of the Celite and the ground glass joint filled with glass beads. The first mobile phase 20% CCl_4; 80% *n*-hexane, elutes the œstrone, the second mobile phase, 15% CCl_4; 11·2% $CHCl_3$; 73% *n*-hexane, elutes the œstradiol, and the third mobile phase, 48% $CHCl_3$; 52% *n*-hexane, elutes the œstriol. The fractions containing the œstrogens were bulked together and dried. In this way it was possible to reduce the interfering material and enhance the œstrogen peaks. The extract which had been greatly purified by this procedure was dissolved in 0·125 ml. 72% methanol, and was ready to be chromatographed on a small column.

This column had a diameter of 0·6 cm. and the Celite was again packed to a depth of 10 cm. 0·1 ml. of the extract dissolved in the stationary phase was applied to some dry Celite on top of the column and the column this time was attached to a syphon calibrated to deliver 1·0 ml. A smaller phase changer was used but the phases and the number of fractions collected remained the same. All the fractions were dried off and fluoresced (Bates and Cohen 1950a and b, Engel et al. 1950). Standards of œstrone, œstradiol-17 β, and œstriol were fluoresced at the same time.

In one case it was found that a woman who had been oophorectomised and adrenalectomised still appeared to be excreting large amounts of œstrogens. The whole of a three-day pool of urine from this woman was therefore hydrolysed and extracted. The extract was subjected to column chromatography. The large column and phase changer were used and 1/6th of the total extract put on to each column. The œstrone sections from each column were bulked together, and the œstradiol and œstriol sections were treated similarly. It was unfortunately not possible to collect sufficient material from the œstradiol and œstriol sections to have a satisfactory bioassay performed on them. Prof. C. J. O. R. Morris, of the Department of Experimental Biochemistry, The London Hospital Medical College, kindly carried out a bioassay of the œstrone fraction, and it was found to possess biological activity which would correspond to the amount of œstrone which had been estimated chemically.

The recovery figures, when 0·2–1·0 μg. œstrone, œstradiol, and œstriol were added to aliquots of urine, were 83% (S.D. 13%), 79% (S.D. 12%), and 75% (S.D. 14%) respectively.

Operative Procedures

Oophorectomy Alone

This was carried out through a lower paramedian incision and an attempt was made to remove as much of the broad ligament as possible with the ovaries.

Bilateral Adrenalectomy

Patients received hydrocortisone (100 mg. intramuscularly) 36, 24, 12, and 3 hours before operation, together with cortisone by mouth (25 mg. 6-hourly) beginning 24 hours before operation. The adrenals were either approached through bilateral loin incisions below or through the bed of the 12th rib, or when the ovaries were also to be removed, the left adrenal gland and ovaries were often approached through a left paramedian incision. In about one-third of these patients a transabdominal bilateral adrenalectomy with oophorectomy was carried out in one stage through a left paramedian incision.

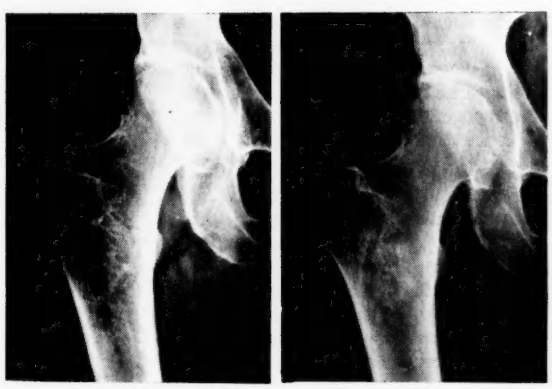
Complications of Surgery

The complications were for the most part similar to those seen after other major operations. One patient with cerebral metastases died from increased intracranial pressure postoperatively. In one case, in spite of the usual preoperative cortisone, severe hypotension developed after operation.

Assessment of Response to Surgery

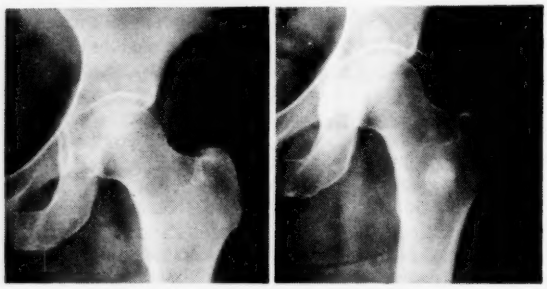
The clinical assessment of results in these patients is full of difficulties. Subjectively the patient often claims considerable symptomatic relief while objectively there is no evidence of response, and for these reasons subjective and objective assessment of results have been kept strictly separate and only the latter is considered in this paper. Objective evidence of remission was judged to be present when a breast tumour diminished in size or an ulcer overlying it became epithelialised. The disappearance of skin metastases and reduction in the size of obvious axillary or supraclavicular glandular metastases have usually allowed a clear-cut decision that the progress of these metastases had been delayed.

Assessing the progress of skeletal metastases proved much more difficult. When an osteolytic bony lesion appeared to undergo definite recalcification radiologically after operation where none existed before, regression was considered to have taken place at that site (fig. 1). Sometimes after adrenalectomy increase in bone density



(a) *(b)*

Fig. 1—Healing of osteolytic secondary in right femur: (*a*) before operation; (*b*) after operation.



(*a*) (*b*)

Fig. 2—Appearance of increased opacity in upper end of femur after adrenalectomy where no lesion was seen before: (*a*) before operation; (*b*) after operation.

appeared radiologically where no lesion had been detected previously. This may have been due to calcification occurring in the vicinity of a previously invisible metastatic deposit but again it may have been due to the development of an osteosclerotic secondary and such lesions were not regarded as evidence of objective response (fig. 2). Reduction in the size of a pleural effusion immediately after operation where frequent paracentesis had been required before, was held to be objective evidence of response (fig. 3).

TABLE I—ASSESSMENT OF RESPONSE TO OOPHORECTOMY AND ADRENALECTOMY

Category	No. of patients	Follow-up (mos.)
Total no. of patients in study	54	4–40
No. of patients showing objective response ..	20	4–40
No. of patients showing no objective signs of response	16	4–13
No. of patients dying within 4 months of surgery	18	0–4
% of all patients showing objective signs of response ..		37%

Abdominal metastases proved difficult to assess but reduction in ascites when frequent tapping had previously been required and reduction in the size of secondary deposits on the pelvic floor were both noticed on occasions and taken as objective evidence of response to surgery. Occasionally objective evidence of regression was seen in one group of metastases, while metastases elsewhere continued to progress. Such a patient was classified as not responding to surgery. In one patient with cerebral metastases, improvement in neurological signs, together with the disappearance of abnormality of the electroencephalogram, was judged as evidence of objective response.

Many authors describe groups of patients in which they think the disease had undergone temporary arrest without actual regression. We have experienced great difficulty in placing our patients with sufficient certainty in such a group. A study of the records of breast-cancer patients not treated by these methods reveals the enormous variations in the manner in which the disease progresses. Thus, one or two distant metastases treated by local radiotherapy may be followed by an interval of years before the next develops. For this reason where no definite objective evidence of regression was measurable by the above methods the patient was considered not to have responded to treatment.

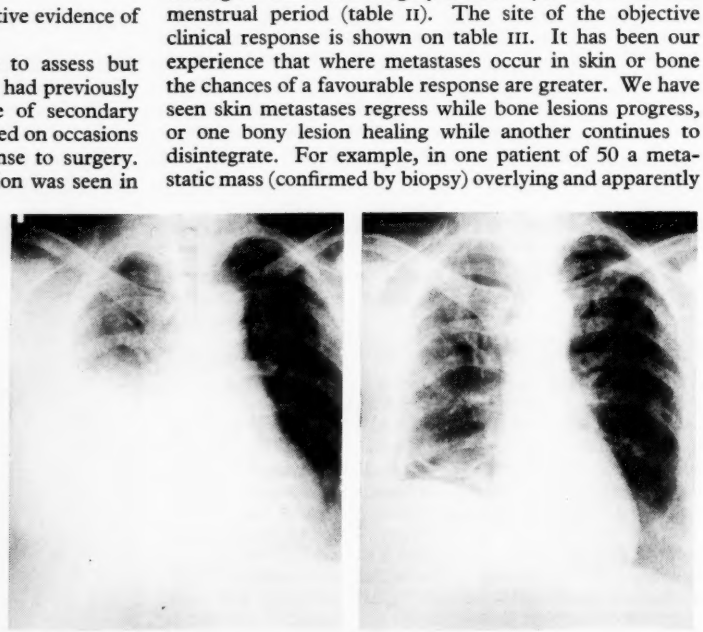
TABLE II—TIMING OF OPERATION

Operation time	Total patients	Response	No response	Dying too early for assessment
Operation premenopausal or within 5 years of last menstrual period	30 (*100%*)	16 (*54%*)	5 (*17%*)	9 (*30%*)
Operation later than 5 years following last menstrual period	24 (*100%*)	6 (*25%*)	9 (*38%*)	9 (*38%*)

As well as a group with clear objective evidence and one with no objective evidence of response after careful follow-up of not less than 4 months, a third group of patients existed who died within 4 months of surgery before satisfactory assessment could be made.

Result of Clinical Assessment

The results of clinical assessment of these fifty-four patients are shown in table I. Twenty-two of the fifty-four patients (37% of the total) produced objective evidence of response, while in fourteen no certain evidence of regression could be seen. Eighteen died within 4 months of operation and most of these patients could probably be considered as not showing a response to treatment. When those patients who obtained definite regression in the disease are compared with those failing to respond, certain differences between the groups are seen, but none of these is statistically significant. Firstly, those responding to treatment were younger (mean age 47·8 years against mean age of those failing to respond 51·1 years) and a higher proportion of them were either premenopausal or had undergone endocrine surgery within 5 years of their last menstrual period (table II). The site of the objective clinical response is shown on table III. It has been our experience that where metastases occur in skin or bone the chances of a favourable response are greater. We have seen skin metastases regress while bone lesions progress, or one bony lesion healing while another continues to disintegrate. For example, in one patient of 50 a metastatic mass (confirmed by biopsy) overlying and apparently



(*a*) (*b*)

Fig. 3—Improvement in pleural effusion after adrenalectomy: (*a*) before operation; (*b*) after operation.

(a) (b)

Fig. 4—Progression of osteolytic secondary in left ilium while skin metastases regressed: (a) before operation; (b) after operation.

fixed to the manubrium sterni with radiographic evidence of destruction of the underlying bone, gradually disappeared after operation (8–10 months). During this period an osteolytic lesion in the left ilium steadily increased in size (fig. 4), while the sternal lesion became denser radiologically.

In another patient aged 38 years numerous metastatic nodules (confirmed by biopsy) scattered widely in the skin of the trunk disappeared gradually during the first few postoperative months. During this period osteolytic lesions appeared in the lumbar spine (detected radiologically) which preoperatively had been radiologically and clinically normal.

Relationship of Preoperative Duration of Metastatic Disease to Response

In most of these patients extensive dissemination had been present for some time before ablative endocrine surgery. The period between the appearance of local recurrence or distant metastases and surgery was shorter in those responding (mean 16 months) than in those failing to respond (mean 34 months), but this difference is not statistically significant.

Duration of Response Achieved

Of the twenty patients judged to have undergone objective regression, nine relapsed within a year of operation. Of the remainder two had relapsed within 2 years and only two had a remission of over 2 years (the varying periods of improvement in the remainder continue at the time of publication).

Results of Urinary Œstrogen Studies

The output of œstrone, œstriol, and œstradiol-17 β in the urine of these patients is given in tables IV and V. There was no significant difference between the preoperative level of responders (table IV) and non-responders, nor were the alterations produced by surgery significantly different in the two groups.

Comment

Our results are not dissimilar to others that have been recorded. Adrenalectomy and oophorectomy will benefit less than 50% of these patients. Too much has been written about the benefits of remission. Even when

TABLE III—RELATIONSHIP OF SITE OF METASTASIS TO OBJECTIVE CLINICAL RESPONSE

Site of metastasis	Total no.	Responders	Non-responders
Skin	22	15	7
Lymph-nodes	20	14	6
Brain	3	1	2
Lung	10	4	6
Peritoneum	3	1	2
Bone	24	14	10

TABLE V—MEANS AND STANDARD ERRORS OF THE MEANS OF URINARY ŒSTROGENS IN 13 PATIENTS RESPONDING AND 5 NOT RESPONDING TO ADRENALECTOMY

—	Improved	Not improved	P
Preoperative total	4·96 ±1·36	5·61 ±2·65	>0·8
,, œstrone	2·27 ±0·67	2·27 ±1·11	>0·9
,, œstradiol	0·464±0·19	0·710±0·32	>0·5
,, œstriol	2·23 ±0·57	2·62 ±1·52	>0·7
Postoperative total	2·22 ±0·60	1·79 ±0·36	>0·6
,, œstrone	1·19 ±0·30	0·82 ±0·078	>0·4
,, œstradiol	0·20 ±0·087	0·11 ±0·010	>0·9
,, œstriol	0·822±0·316	0·882±0·28	>0·9

TABLE IV—URINARY OUTPUT (μg. per 24 hr.) OF ŒSTRONE, ŒSTRADIOL, AND ŒSTRIOL PATIENTS SHOWING OBJECTIVE EVIDENCE OF RESPONSE

Patient	Specimen		Œstrone	Œstradiol	Œstriol	Total
		months				
1	Preoperative		9·8	2·66	6·48	18·94
	Postoperative	9	3·25	<0·1	4·05	7·40
		16	4·97	1·14	4·57	10·68
		20	6·90	0·25	6·06	13·21
2	Preoperative		2·05	0·19	6·48	8·72
	Postoperative	2	2·81	1·20	1·60	5·61
		9	1·40	<0·1	1·45	2·95
		11	0·96	<0·1	<0·1	<1·16
3	Preoperative		1·47	0·62	0·69	2·78
	Postoperative	1	0·15	<0·1	<0·1	<0·35
		11	0·29	<0·1	<0·1	<0·49
4	Preoperative		2·86	0·37	1·01	4·24
	Postoperative	5	1·35	0·13	0·65	2·13
		11	0·62	0·11	0·51	1·23
		13	0·48	0·11	0·18	0·77
		18	0·88	<0·1	<0·1	<1·08
5	Preoperative		0·98	0·33	<0·1	1·41
	Postoperative	7	1·72	0·23	0·16	2·11
6	Preoperative		0·35	<0·1	1·05	1·50
	Postoperative	2	0·11	<0·1	0·2	<0·41
7	Preoperative		2·85	0·66	2·7	6·21
	Postoperative	6	0·71	<0·1	<0·1	<0·91
		9	0·90	<0·1	0·26	<1·26
		14	0·54	<0·1	0·13	<0·77
8	Preoperative		2·74	0·25	2·83	5·82
	Postoperative	3	0·24	<0·1	0·29	<0·63
		11	0·78	<0·1	0·31	<1·19
9	Preoperative		0·89	0·19	1·59	2·67
	Postoperative	2	0·80	<0·1	0·19	1·09
		7	1·10	<0·1	<0·1	<1·3
10	Preoperative		1·26	<0·1	0·85	2·21
	Postoperative	2	0·19	<0·1	0·29	0·58
11	Preoperative		0·6	<0·1	1·0	1·7
	Postoperative	3	2·4	<0·1	1·07	3·57
12	Preoperative		1·45	0·33	1·49	3·27
	Postoperative	1	1·47	0·16	<0·1	1·73
		4	0·84	0·15	<0·1	1·09
13	Preoperative		2·22	0·13	2·7	5·05
	Postoperative	4	0·32	<0·1	1·88	2·30
	PATIENTS SHOWING NO OBJECTIVE EVIDENCE OF RESPONSE					
1	Preoperative		0·48	0·12	0·44	1·04
	Postoperative	5	0·82	<0·1	0·77	<1·6
2	Preoperative		0·89	<0·1	<0·1	<1·09
	Postoperative	2	0·57	<0·1	<0·1	<0·77
3	Preoperative		0·74	1·82	3·44	6·0
	Postoperative	2	0·86	<0·1	0·53	<1·49
4	Preoperative		2·91	0·62	0·88	4·41
	Postoperative	9	0·58	<0·1	1·46	2·14
5	Preoperative		6·35	0·89	8·25	15·49
	Postoperative	3	1·26	0·15	1·55	2·96
		6	0·52	<0·1	0·31	0·92

younger patients are chosen and metastases are in the more favourable sites probably a 40% remission-rate is an optimistic assessment and indeed remission at one site may be associated with progression elsewhere—if the patients are studied intensely enough. And what of this group undergoing regression of disease? While there were long remissions of 2 years and more in this series, they were exceptional. All too often within 6–8 months there was evidence of fresh progress either at the old sites or in new metastatic deposits. Any humane clinicians treating a large series of these patients have their beds inundated with such relapsing patients, to say nothing of those who fail to respond and remain hospital patients to the end.

Clinical methods appear of little help in selecting patients for endocrine surgery but it seems desirable to exclude older patients and those with metastases in unfavourable sites like the central nervous system. Those with metastases in skin and bone seemed to respond more often and probably the sooner endocrine surgery is performed after the disease becomes generalised the better, since this interval was much shorter in those responding. Although the numbers were not sufficient to make this difference significant statistically, it is interesting that a similar trend was seen in another series (McAllister et al. 1960). Lengthy measurements of the urinary œstrone, œstriol, and œstradiol-17 β by a method which can detect as little as 0·1 μg. in the 24-hour urine pool have failed to show any significant differences by which selection could be made and there appears little gain in continuing their measurement in the urine of such patients.

Like Smithers (1960), we are impressed by the infrequency with which objective responses are obtained in these patients of sufficient duration to make hospital care and major surgery worth while. Only the memory of a few striking responses of long duration encourages the surgeon to continue treating the disease at this stage. If further critical evaluation showed that oophorectomy and cortisone could achieve similar results there would be a strong case for discontinuing hypophysectomy and adrenalectomy at present. Indeed, the results of stilbœstrol and testosterone therapy may not be greatly inferior to surgical ablation and far less disturbing for the patient; and in this connection the studies coordinated by Segaloff (1960) will be of great importance.

If prognostic criteria were found allowing the surgeon to select only those likely to benefit from endocrine surgery the position might be altered. Further reports on the urinary levels of 17-hydroxycorticosterone and æthicocholanolone of such patients will be awaited with interest, and perhaps the measurement of other œstrogens may prove profitable. Another approach is to look for differences in uptake of labelled œstrogens by the tumour tissue. In some of the patients in this series this proved possible and the results are recorded in the accompanying paper.

We have to thank the many clinicians of The London Hospital who allowed us their patients for this study and Prof. V. W. Dix for his encouragement and help.

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STUDIES WITH TRITIUM-LABELLED HEXŒSTROL IN ADVANCED BREAST CANCER

Comparison of Tissue Accumulation of Hexœstrol with response to Bilateral Adrenalectomy and Oophorectomy

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It now seems well established that neither the preoperative nor postoperative levels of urinary œstrone, œstradiol 17β, or œstriol show any correlation with response to adrenalectomy and oophorectomy for advanced breast cancer (Bulbrook et al. 1958, McAllister et al. 1960, Swyer et al. 1961, Irvine et al. 1961). This does not necessarily mean, however, that response to the operation is independent of œstrogen metabolism; and this matter is discussed in an accompanying paper (Irvine et al. 1961).

It has therefore seemed worth investigating the capacity of tumour tissue to accumulate a labelled œstrogen and to attempt to correlate this accumulation, if any, with the clinical response to adrenalectomy and oophorectomy.

Glascock and Hoekstra (1959) showed that when labelled hexœstrol was given to female goats and sheep in physiological doses (1 μg. per kg. body-weight) the highest concentration of radioactivity occurred in those organs which respond to œstrogens. These concentrations (taking that in muscle as unity) varied from about 10 (ovaries, oviducts, mammary glands) to 20 (uterus and vagina). The accumulation was only brief, reaching a maximum 5 hours after injection and declining to negligible values within 12–24 hours. It was further shown by Burgos-Gonzalez and Glascock (1960) that the radioactivity in the genital organs was due almost entirely

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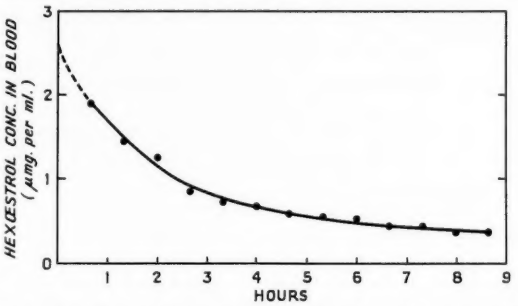

Rate of decline of blood specific activity (expressed as hexœstrol concentration) after intravenous injection of 100 μg. tritiated hexœstrol.

to hexœstrol itself both free (70–90%) or conjugated (10–30%).

So far tissue accumulation has been studied in ten cases undergoing bilateral adrenalectomy and oophorectomy. In two of them and in a further four undergoing radical mastectomy, the concentration of hexœstrol in the blood was determined in samples taken at twenty-minute intervals up to the time of operation.

The work continues but we feel that the results so far obtained justify this preliminary communication. For the purpose of calculation, the radioactive compound in the samples is presumed to be hexœstrol itself, and will be referred to as such. This is to some extent justified by the work on the sheep (Burgos-Gonzalez and Glascock 1960).

Experimental Details

Only patients with palpable cutaneous metastases were studied for ease of biopsy and to ensure that at least one feature of the disease could be assessed with reasonable certainty after the operation. The clinical assessment was as described by Irvine et al. (1961).

The hexœstrol believed to be labelled in stable position was prepared as described by Glascock and Pope (1960) and had a specific activity of 10 μC per μg. (about $2{\cdot}5 \times 10^7$ counts per min. per μg. in our equipment). A dose of 100 μg. was given intravenously to each patient as a dilute solution (50 μg. per ml.) in isotonic saline six hours before the operation. This interval was chosen because it had been shown that the concentration of hexœstrol in the blood would then have fallen to a small value and the contribution of hexœstrol in the blood included in the tissue samples would therefore be a small part of the total. Furthermore, by this time the concentration of hexœstrol in the blood was changing less rapidly than at earlier times, and unavoidable delays in the operation might be less critical.

At the beginning of the operation samples of striated muscle, blood, and metastatic tumour tissue (usually from superficial sites) were taken. The identity of the metastasis was always confirmed histologically. In the experiments designed to show the changing concentration of hexœstrol in the blood after the injection, 1 ml. samples were taken into citrate every 20 minutes.

Assay.—All samples, including whole blood, were freeze dried, tissue samples being first blotted with gauze, dissected as free as possible from fat, skin, and fibrous tissue, and homogenised. Tritium was determined in the well-mixed dry tissue by a combustion and gas-counting method (Glascock 1954) and nitrogen by the Kjeldahl method. The concentration of hexœstrol in the tissue, calculated from its tritium content, was finally expressed as mμg. per g. nitrogen, thus eliminating the diluting effect of fat which is known not to accumulate hexœstrol (Glascock and Hoekstra 1959).

Results

Concentration of Hexœstrol in Blood

The concentration of hexœstrol in blood taken at intervals after the injection is shown for one of the six patients in the accompanying figure. By extrapolating the curve back to zero time the initial concentration in the blood of this patient is found to be 2·6 mμg. per ml. and in the blood of the others from 2·4 to 4·6 mμg. per ml. If the 100 μg. injected were confined to the blood (say, 4·5 litres for a person of 70 kg. body-weight) the initial concentration would be 22 mμg. per ml. whereas if distributed throughout the whole body water (say 50 litres) the concentration would be about 2 mμg. per ml. The initial concentrations actually found are therefore consistent with rapid loss of the dose from circulation into the general body water although we have so far no direct evidence that this is so.

Of the six patients investigated, two underwent bilateral adrenalectomy and oophorectomy at a later date and subsequently showed objective evidence of improvement. The other patients underwent only radical mastectomy. The concentration/time curves are approximately exponential in form but so very similar in slope that it seems unlikely that this method will indicate any biochemical or physiological differences between the patients who respond to the operation and those who do not.

Concentration in Tissues

In the table are shown the concentrations of hexœstrol in muscle, blood at the time of the operation, and tumour. The range for muscle (8·6–25·7 mμg. per g. N) is relatively about the same as that for blood (13–40 mμg. per g. N) although the higher concentrations in muscle do not occur in the same patients as the higher concentrations in blood. The range of concentration in tumour tissue, however, is very much greater (10–146 mμg. per g. N) than in muscle and blood and it will be seen that the

CONCENTRATION OF HEXŒSTROL IN TISSUES AT OPERATION 6 HOURS AFTER INTRAVENOUS INJECTION OF 100 μG.

Expt. no. and subject	Tissue	Hexœstrol concn. (mμg. per g. N)	Ratio: Hexœstrol tumour/muscle	Clinical response
9	Tumour	23·6	0·92	No improvement
	Muscle	25·7		
	Blood	40·7		
14	Tumour	24·6	1·0	No improvement
	Muscle	24·0		
	Blood	17·9		
15	Tumour	23·1	1·9	No improvement
	Muscle	12·3		
	Blood	18·7		
16	Tumour	10·7	0·86	No improvement
	Muscle	10·4		
	Blood	12·5		
19	Tumour	17·9	1·8	No improvement
	Muscle	10·2		
	Blood	24·3		
22	Tumour	23·3	2·4	No improvement
	Muscle	9·6		
	Blood	27·8		
5	Tumour	146·0	9·3	Improved
	Muscle	15·7		
	Blood	17·5		
7	Tumour	85·0	6·0	Improved
	Muscle	14·1		
	Blood	35·3		
8	Tumour	34·6	3·0	Improved
	Muscle	11·0		
	Blood	13·3		
12	Tumour	58·5	6·7	Improved
	Muscle	8·7		
	Blood	34·9		

patients form two groups: those with high concentrations (34·6–146 mμg. per g. N) who improved after the operation and those with lower concentrations (10·7–24·6 mμg. per g. N) who did not.

The difference between the two groups is even more marked when the concentration of hexœstrol in tumour is expressed as a ratio to that in muscle—which may reasonably be taken as a control tissue. As shown in the table, this ratio was 3·0–9·3 in patients who improved after the operation and 0·86–2·4 in those who did not.

Discussion

It is obvious that many more cases will have to be studied before we can say with confidence whether or not those patients benefiting from oophorectomy and adrenalectomy are those whose tumours uniformly have a high capacity to accumulate hexœstrol. If further studies show a similar pattern, this method might prove of use in the selection of patients for endocrine surgery. Such a method of selection would only be of use in patients with superficial metastases and it must be admitted that the method is time-consuming and exacting. With larger doses of radioactivity, simpler methods of counting may prove applicable.

Several improvements in technique are under consideration. For example, no correction has been made in the result reported here for the hexœstrol contained in the blood included in the tissue samples, nor indeed for the contribution of that blood to the total nitrogen of the samples. This correction could be made if the blood content of the tissues were measured by means of ^{51}Cr-labelled red corpuscles injected long enough before the operation to have mixed completely with the circulating blood. The correction is likely to be small, however, because in experiments on goats this technique has shown that the blood content of most tissues was less than 5%, only lung (17%) being much higher.

Summary

Tritium-labelled hexœstrol was injected intravenously in ten patients with advanced breast cancer and the concentration at the time of bilateral adrenalectomy and oophorectomy studied in muscle, blood, and tumour tissue.

In those subsequently showing objective evidence of response (four patients) the concentration in tumour tissue was higher than in muscle, the ratio varying between 3·0 and 9·3.

In those failing to show such evidence this ratio was lower, varying between 2·4 and 0·86.

In six patients with breast cancer blood concentration-time curves were plotted after a similar injection. These were very similar in form.

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LIPÆMIA AND BLOOD-COAGULATION DEFECTS IN RELATION TO ISCHÆMIC HEART-DISEASE

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DEATHS due to ischæmic heart-disease are still increasing (Registrar General 1959), and the increase is as yet unexplained. The need for further research into the causes, mechanisms, and treatment of this disease is therefore obvious.

Many causal factors have been and are suspected, but there is insufficient evidence to incriminate any particular one (Morgan 1956). The problem is further confused by the fact that, although coronary atherosclerosis is a prerequisite of coronary heart-disease, according to Morris (1951) the incidence of coronary atherosclerosis itself has decreased during the last fifty years. This suggests that, as Macfarlane (1955) pointed out, the solution to the problem is more likely to be found in changes in the blood than in the coronary tree itself. Neither the anatomy of the coronary arteries nor the dynamics of the blood flowing through them is likely to have changed in the last twenty years or so. The composition of the blood, on the other hand, is known to change with alterations of diet, and the victims of this disease may be the ones whose defective coagulation and fibrinolytic systems, normally in equilibrium (Astrup 1956), are unable to adjust themselves to the new conditions. Many workers (e.g., Fullerton 1953, O'Brien 1955, and Maclagan and Billimoria 1956) have in fact shown that ingestion of fat may shorten the 'Stypven' (Russell-viper venom) clotting time, while Greig (1956), Kwaan (1957), and Billimoria et al. (1959) have demonstrated that it reduces fibrinolysis in blood. A relationship of this kind also accords well with the Duguid (1946) theory of the pathogenesis of atherosclerosis, since he has shown that the deposition

TABLE I—SUBJECTS STUDIED

Group	No.	Age		Mean age (yr.)
		Min.	Max.	
1. Normal controls				
Male	20	40	68	53
Female	11	41	69	56
2. Angina pectoris				
Male	20	44	75	59
Female	4	56	67	62
3. Myocardial infarction				
Male	28	42	72	58
Female	9	41	70	61
4. Miscellaneous diseases				
Diabetes mellitus ..	14	40	80	58
Hypertension	16	40	67	55
Xanthomatosis ..	13	30	61	40
Hyperthyroid ..	6	25	70	52
Hypothyroid	6			

of fibrin on blood-vessel walls may be important in promoting this condition.

This paper compares plasma lipæmia and coagulation and blood fibrinolytic levels in normal subjects with those in patients who have ischæmic heart-disease. A small series of other patients, with diseases commonly associated with coronary disease, has been similarly investigated.

Subjects and Methods

The subjects under investigation were divided into four main groups: (1) normal controls, (2) angina pectoris, (3) myocardial infarction, and (4) miscellaneous diseases. Table I shows numbers and ages.

The groups were tested under fat-free conditions, and a number of subjects in groups 1, 2, and 3 were also tested on a later day after a fat test-breakfast. In addition, the effects of anticoagulants on the myocardial-infarction group were investigated.

Group 1.—The normal controls were members of the hospital staff, some other volunteers, and a small number of hospital patients with conditions not thought to influence coagulation or fibrinolysis. None showed any evidence of diabetes mellitus, xanthomatosis, thyroid disease, or nephrosis —diseases particularly associated with altered blood-lipid pattern and often with severe atherosclerosis. Electrocardiograms were obtained from all but 3 subjects and were within normal limits.

Group 2 were patients attending the cardiac department of Westminster Hospital who had a typical clinical history of angina pectoris but no evidence of complicating disease.

Group 3.—The myocardial-infarction subjects comprised patients from the hospital and from the practice of D. W., all having a clear clinical history of myocardial infarction and in most cases an electrocardiogram showing characteristic changes. A small number (3) whose electrocardiograms were equivocal were included because the clinical evidence of infarction was strong, but they may be subjects with acute coronary insufficiency.

Group 4.—The miscellaneous-diseases group consisted of patients at the hospital with the conditions listed in table I.

While all effort was made to carry out the tests before treatment was begun this was not always possible. Some of the patients were therefore under treatment except on the morning of the test, when all drugs were omitted. However, no patient receiving anticoagulant therapy was included except those in the myocardial-infarction group who were being investigated for anticoagulant effect. The subjects were all having a normal diet. In the myocardial-infarction group the interval between infarction and the test was usually between six weeks and three years; a few subjects in whom the interval was less than six weeks showed no significant difference from the main group.

General Procedure

Our previous work has shown that venous stasis, diurnal variation, butter feeding, and exercise all markedly influence fibrinolysis (Billimoria et al. 1959). The subjects tested under fat-free conditions were therefore given a test breakfast at 7.15 to 7.30 A.M., consisting of bread or toast without fat of any kind, jam or marmalade being allowed and tea or coffee without milk, sugar being allowed. For the fat breakfast a similar meal was given, containing in addition $1^1/_2$ oz. (42 g.) of butter. Smoking and drugs were not allowed on the morning of the test.

Blood was taken at 9.30 A.M. and 11.30 A.M. (two and four hours after feeding), the subjects being rested for at least half an hour first. It was taken with minimal stasis, using the two-syringe (siliconed) technique and was diluted immediately with ice-cold buffer. Where a comparison of pre-butter and post-butter effect was required, the subjects were tested on two successive days wherever possible.

Technical Methods

Plasma was separated by centrifugation at 4°C for ten minutes at 3500 g. *Plasma turbidity* or *lipæmia* was measured in arbitrary units in 3 ml. tubes on a nephelometer,* using a turbidity standard supplied by the makers. *Stypven clotting time* was measured, using the "instantaneous" method of Maclagan, Billimoria, and Curtis (1958) in which stypven and calcium chloride are added simultaneously to the plasma and the clotting time is determined.

Fibrinolysis was measured on whole blood by the method of Billimoria et al. (1959), which was developed from that of Fearnley et al. (1957). In our method the rate of lysis of the clot is followed by means of hourly estimations of its hæmoglobin content, and the time for 50% lysis is determined graphically. Hourly estimations were made, up to six hours. Where clots did not lyse within that time the lysis time was assumed, for statistical calculations, to be six hours.

Results

Tests under Fat-free Conditions

The three groups—normal, angina pectoris, and myocardial infarction—were tested at 9.30 A.M. and 11.30 A.M. Table II shows that the lipæmia at 9.30 A.M. is significantly higher and the stypven time significantly shorter in both angina and infarction groups than in the controls. The 50% lysis time is significantly longer in the angina group than in the normals, but there is no significant difference between the infarction group and the normals. The differences between the angina and infarction groups are not statistically significant. In view of the possible relation of these results to age and sex, the normals were also compared with the two pathological groups in figs. 1–4, where these factors are indicated.

Fig. 1 compares lipæmia in normal, angina, and infarction groups. It shows that the higher lipæmia mean in both angina and infarction groups is not related to the age of the subjects. The graph also shows that, in spite of these average changes, many of the angina and infarction readings are within the normal range. The lipæmia readings of each group are consistently higher in the normal males than in the normal

*Evans Electroselenium Ltd., Harlow, Essex.

TABLE II—COMPARISON OF FAT-FREE RESULTS IN NORMAL, ANGINA PECTORIS, AND MYOCARDIAL INFARCTION (MEAN ± STANDARD ERROR)

Group	9.30 A.M.			11.30 A.M.		
	Lipæmia (units)	Stypven time (sec.)	50% Lysis time (hr.)	Lipæmia (units)	Stypven time (sec.)	50% Lysis time (hr.)
1. Normal	21·75 ± 1·22	31·0 ± 1·19	3·50 ± 0·24	22·4 ± 2·01	27·4 ± 1·78	2·82 ± 0·16
2. Angina pectoris	36·2 ± 4·45	24·4 ± 0·97	4·47 ± 0·33	36·28 ± 6·65	22·4 ± 1·31	3·38 ± 0·22
Significance of differences: normal-angina total	P < 0·001	P < 0·001	P < 0·02	N.S.	P < 0·02	P < 0·02
3. Myocardial infarction	31·1 ± 2·96	27·4 ± 1·20	3·66 ± 0·23	28·7 ± 2·07	26·0 ± 1·65	2·53 ± 0·13
Significance of differences: normal-infarction	P < 0·001	P < 0·02	N.S.	P < 0·02	N.S.	N.S.
Angina-infarction	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

N.S. = not significant.

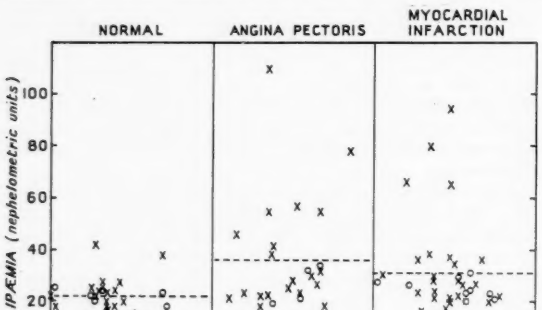

Fig. 1—Lipæmia (plasma turbidity) after fat-free breakfast.

females, the sex difference being statistically significant, $P < 0.02$.

Fig. 2 shows a comparison of stypven time in normal, angina, and infarction groups. Again the shorter stypven time in the pathological groups is not related to age. Again there is an overlap of readings between the three groups, and in the infarction group the shorter stypven time is predominantly seen in the male subjects.

Fig. 3 illustrates the correlation between stypven time and lipæmia in the complete series of cases. The correlation between the two factors is significant ($r = -0.65$) and the drop in stypven time is therefore at least partly a measure of lipæmia.

Fig. 4 shows the relation between 50% lysis time in the three groups at 9.30 A.M., after a fat-free breakfast. This emphasises the higher 50% lysis time in the angina group compared with normal while the infarction group approximates to the normal mean. The higher mean for the angina group is partly due to the greater number of blood-clots not lysing within six hours; so the actual mean 50% lysis time for both angina and infarction groups would have been higher if the *actual* lysis times of these clots had been used in the calculations. Once again, these differences are not dependent upon age. In normal subjects lysis times between four and five hours were very infrequent, suggesting the possibility of a bimodal distribution (see below).

The important effects of anticoagulants on 50% lysis time are shown in fig. 5. It was difficult to obtain, for comparison, the necessary number of early cases not on anticoagulants; but 10 patients whose stypven time was longer than 45 sec. were accepted as being satisfactorily anticoagulated (9 on phenindione; 1 on heparin). The patients were tested under the usual fat-free conditions and bled at 9.30 A.M. The group on anticoagulants had a significantly shorter 50% lysis time (2·9 hr. ± S.E. 0·3) than the group not on anticoagulants (3·6 hr. ± S.E. 0·23). The lipæmia was also slightly reduced in the group on anticoagulants.

Results after Fatty Breakfast

Tests were repeated after a fat breakfast, as described above, in a proportion of subjects with angina and infarction. In the normal group, fat feeding produced a greater lipæmia and a shorter stypven time at two hours than at four hours. The 50% lysis time was longer at four hours but not at two hours after the fatty meal.

In the angina group the lipæmia was maximal at four hours but the greatest shortening of the stypven time and lengthening of the 50% lysis time occurred at two hours post-fat. The infarction group showed maximal lipæmia at four hours with a slight shortening of the stypven time, but the 50% lysis time was lengthened at two hours only. Thus the lipæmia is maximal at two hours post-fat in the normal group but in the angina and infarction groups it was maximal at four hours. The effect on stypven time does not always coincide with maximal visible lipæmia, while the 50% lysis time appears to have no relation to the visible lipæmia levels.

On the whole, the results of the fat-feeding experiments conformed to expectations, but it did not add enough new information to justify the continuation of this more time-consuming test.

TABLE III—COMPARISON OF NORMAL CONTROLS AND MISCELLANEOUS GROUPS TESTED (MEAN ± STANDARD ERROR)

Group tested	Lipæmia (turbidity units)	Stypven time (sec.)	50% Lysis time (hr.)
Normal controls	21·7 ± 1·22	31·0 ± 1·19	3·5 ± 0·24
Hypertension	26·1 ± 1·79	28·7 ± 1·72	4·7 ± 0·44
Significance of difference from normal mean	P < 0·02	N.S.	N.S.
Diabetes mellitus	24·14 ± 1·9	31·07 ± 0·36	3·46 ± 0·41
Significance of difference from normal mean	P < 0·02	N.S.	N.S.
Xanthomatosis	69·9 ± 16·3	26·32 ± 1·48	4·50 ± 0·52
Significance of difference from normal mean	P < 0·001	P < 0·01	N.S.
Thyroid group			
Hyperthyroid	19·25 ± 0·55	29·6 ± 2·20	3·48 ± 0·79
Hypothyroid	36·12 ± 8·88	28·8 ± 1·5	4·50 ± 0·424
Significance	N.S.	N.S.	N.S.

MISCELLANEOUS DISEASES

Certain other groups were tested similarly under fat-free conditions at 9.30 A.M. Table III shows the results.

Significantly increased lipæmia was found in all the first three pathological groups, but only in the xanthomatosis group was there any accompanying shortening of stypven time. No group showed any statistically significant changes of the 50% lysis time although a slight lengthening was found in the hypertensive group. The thyroid group showed a wide scatter in all results with no significant differences from the normal. The hyperthyroid and hypothyroid groups were also contrasted with each other, but again no significant difference was found.

Discussion

In our tests patients with angina pectoris, myocardial infarction, and xanthomatosis had abnormally high mean values for fasting plasma turbidity. A smaller but significantly increased lipæmia was also found in hypertensive and diabetic patients. Similar comparative differences were found when the normal angina and infarction groups were given a fatty meal.

These results are in conformity with those previously reported by Barritt (1956), Mitchell and Bronte-Stewart

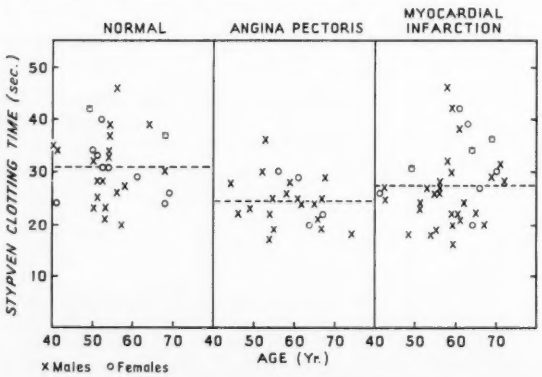

Fig. 2—Stypven time after fat-free breakfast.

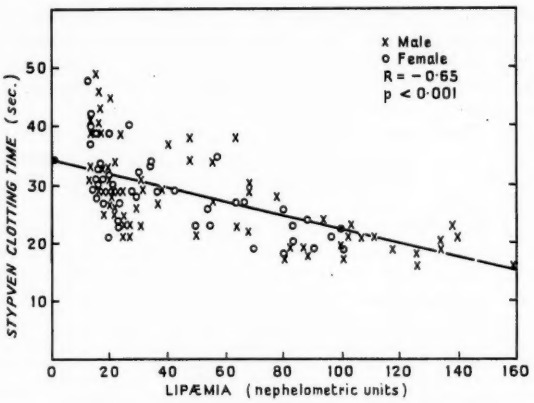

Fig. 3—Correlation of lipæmia with stypven time in complete series. $r = -0{\cdot}65$. $P<0{\cdot}001$.

(1959), and Bouchier and Bronte-Stewart (1961) except that in our series the peak lipæmia in the normal group was at two hours post-fat, whereas Barritt found it at three hours and Bronte-Stewart at four. The differences may well be due to the nature of the meal given. Thus our fat breakfast contained 42 g. of butter, that of Barritt 60 g. in the form of double-cream milk, and that of Bronte-Stewart 75 g. as double-cream, butter, and three eggs. Our meal might be considered more physiological, and indeed contained the maximum amount of butter which could be eaten by our more sensitive subjects without discomfort.

In our series the stypven time was used as a measure of changes in the coagulation system, and we were able to demonstrate that it was correlated with lipæmia, as stated by Fullerton et al. (1953) and O'Brien (1955). Under fasting conditions the clotting time in our angina and infarction groups was significantly shorter than in our controls. After a fat meal it was shortened further in all three groups, but less in the pathological groups than in the normals. The decreased response to butter shown by the cardiac groups seems to depend on their lower initial stypven times, since the maximal response, corresponding to a stypven time of about 15 seconds, was similar in all the groups.

These results are to some extent in agreement with those

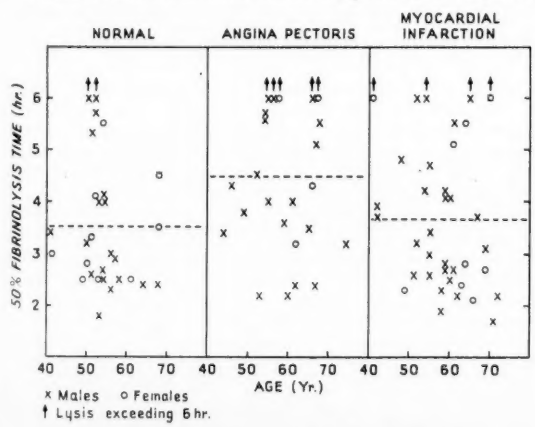

Fig. 4—Fibrinolysis times after fat-free breakfast.

of McDonald and Edgill (1959), who showed that the stypven time was shorter in angina pectoris than in normal subjects and was shorter in myocardial infarction than in angina. Our results, on the other hand, were more abnormal in angina than in infarction. Merskey et al. (1960), however, using a battery of coagulation tests, could not detect any difference between white controls and white "coronary" subjects—here again the fat content of the breakfast was "minimal" but not measured. In Merskey's study the coronary group included a mixture of angina and infarction patients in unstated proportions, and thus any possible difference between the two latter groups was not allowed for. O'Brien (1955) also reported negative results with the stypven test. In both these studies an interval was allowed between the addition of stypven and calcium chloride solution, which we regard as undesirable (see methods).

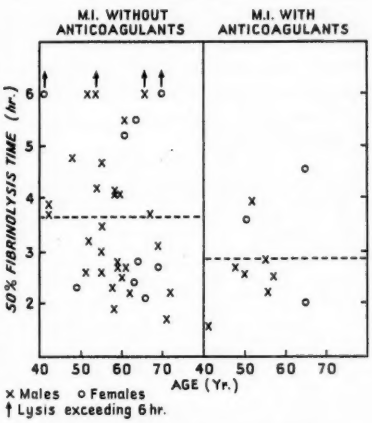

Fig. 5—Fibrinolysis time in relation to anticoagulant therapy in cases of myocardial infarction (M.I.).

Our results after the fat breakfast showed a general correlation between the visible lipæmia and the stypven time, but the two effects were often greatest at different times, suggesting that the effect of lipæmia on the stypven time is not confined to the visible lipids.

As regards fibrinolysis, our results show a more striking prolongation of the 50% lysis time in angina than in infarction, which was quite unexpected. A similar prolongation of fibrinolysis was reported by Hume (1958) during the first week after myocardial infarction: Merskey et al. (1960), on the other hand, found no significant differences in fibrinolysis time between their cardiac patients and their normal controls. A similar depression of fibrinolysis has been noted by Nestel (1959) in intermittent claudication. Apart from the difference in patients studied (as noted above), the methods used for determining fibrinolysis time differed from ours in some important respects. Antonis and Bersohn (1961) have pointed out the inadequacies of certain methods for the measurement of fibrinolysis, especially where repeated estimations are involved. Our present method employs controlled conditions and eliminates subjective factors; it has given consistent results on normal subjects studied over a period of three years, although some patients with myocardial infarction have shown larger fluctuations.

The apparent bimodality of the normal group with respect to fibrinolysis has been mentioned. It may possibly depend on the existence of two different fibrinolytic systems, one being rapid and labile and the other slow but more stable, as suggested elsewhere (Billimoria et al. 1959). If so, the labile factor must be almost absent in the people with the longer lysis times (over five hours), who are particularly prominent in the two cardiac groups.

Anticoagulant therapy caused a significant shortening

of the 50% lysis time and a small decrease in lipæmia. Similar results in heparin-treated patients have been briefly reported by Lackner and Merskey (1959). Anticoagulants therefore seem to serve a dual purpose, their anticoagulant action being associated with increased fibrinolytic activity.

Like most other investigators, we have studied patients with myocardial infarction only after that event (usually six weeks to three years after it) and we cannot be sure that the changes we found were present before infarction. Dodds and Mills (1959) showed considerable changes in serum lipids and lipoproteins in the weeks following myocardial infarction; if there are similar changes in the fibrinolysis time, our results could have been influenced by them. On the other hand, in most of our cases enough time had elapsed to eliminate the acute effects of the infarction.

Taken as a whole, our results suggest that, in a proportion of patients with ischæmic heart-disease, lipid metabolism deviates significantly from normal, and that the deviations have an appreciable effect on blood coagulation and blood fibrinolysis. Somewhat similar changes were evident in xanthomatosis, and to a lesser extent in hypertension and diabetes mellitus—three conditions which are known to predispose to coronary disease. It should be noted, however, that our findings in the pathological groups include many normal figures. Indeed, in spite of the significance of the mean of the results, the actual number of patients exhibiting frankly abnormal tests is small. Similar considerations, of course, apply to all other estimations so far explored in atherosclerosis—e.g., the blood-cholesterol and lipoprotein levels. Obviously the factors discussed can have ætiological significance in only a proportion of the cases investigated.

The mechanism underlying the changes described is at present unknown, and they could be related to ischæmic heart-disease in more than one way. For example, they might promote primary thrombosis—a mechanism of coronary occlusion recently emphasised by Crawford et al. (1961). They could also be held to support the hypothesis that atheroma is a sequel to repeated arterial thrombosis (Duguid 1946). The observations on lipæmia could also be reconciled with the older infiltration theory of atheroma (Ribbert 1904, Aschoff 1907). Further work will be needed to determine which of these relationships is the most important; but they do not, of course, exclude one another.

Summary

1. In 31 normal subjects, levels of plasma lipæmia (plasma turbidity), ' Stypven ' clotting time, and whole-blood fibrinolysis time (50% lysis time) were determined under fat-free and post-fat conditions ($1^1/_2$ oz. butter). These values were compared with those of 24 patients having angina pectoris, 37 with myocardial infarction, and 14 with diabetes mellitus, 16 with hypertension, 13 with xanthomatosis and 12 with thyroid disease.

2. Under fat-free conditions the angina group showed a significantly higher lipæmia, longer fibrinolysis time, and shorter stypven time than the normal. The infarction group showed increased lipæmia and a significantly shorter stypven time than the normal; there was an increase in fibrinolysis time which was not statistically significant.

3. After fat feeding, the normal group showed maximal lipæmia and maximal shortening of stypven time two hours post-fat with maximal increase of 50% lysis time four hours post-fat. In the angina group the lipæmia was maximal after four hours, but the maximal shortening of stypven time and increase of 50% lysis time occurred at two hours post-fat. The infarction group showed maximal lipæmia and slight shortening of the stypven time after four hours, but maximal increase of 50% lysis time occurred two hours after the fatty breakfast.

4. There was a general correlation between visible lipæmia and stypven time, but the two effects were often greatest at different times. Anticoagulants stimulated fibrinolysis.

5. In hypertension, xanthomatosis, and diabetes mellitus there was an increased lipæmia, and patients with xanthomatosis also had a shorter stypven time. The 50% lysis time was normal in all these groups.

We are indebted to many of the medical and surgical staff of the Westminster Hospital Group for access to patients, to Dr. E. Jepson for referring cases of familial hypercholesterolæmic xanthomatosis, and to Mr. G. J. Copplestone for help with the hospital records.

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A NEW MUCOLYTIC AGENT BY AEROSOL FOR INHALATION IN CHRONIC BRONCHITIS

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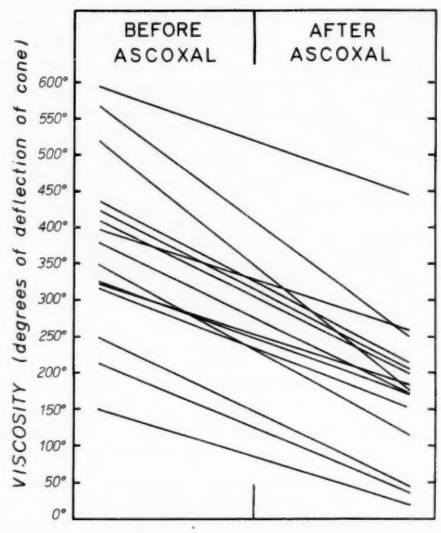
BECAUSE expectorants are disappointing in increasing the amount of sputum or reducing its viscosity, interest has been shown recently in substances which reduce sputum viscosity by a direct physical or enzymatic action when given by aerosol-inhalation (*Lancet* 1957).

There are two distinct types of sputum: " mucoid ", which is clear, highly viscid, and adhesive; and " purulent ", which is opaque, yellow, and less viscid. Mucoid sputum consists of water, mucopolysaccharides, and mucoprotein (Brogan 1959) and its viscosity depends upon the relative amounts of these constituents (Cragg and Smith 1961). Purulent sputum consists of bundles of parallel fibres of desoxyribonucleoprotein derived from the nuclei of degenerated pus cells (Armstrong and White 1950). Frequently these two types are mixed, but the viscidity and adhesiveness of mucopurulent sputum is due to its " mucoid " content. Purulence of sputum can usually be controlled by suitable antibiotics, but the viscosity and amount of mucoid sputum is not reduced by antibiotics (May 1953). Moreover, the patient may actually feel worse when the sputum becomes mucoid after being purulent because mucoid sputum is sticky and difficult to expectorate, and because of its high viscosity it is often retained in the lungs. This is especially liable to occur in chronic



Effect of ascoxal aerosol on viscosity of sputum.

bronchitis (Oswald 1954), the aged, and after abdominal operations (Palmer and Sellick 1953). To reduce the viscosity of mucoid sputum, aerosols of proteolytic enzymes, trypsin and chymotrypsin, and detergent solutions (the commonest being 'Alevaire') have been used. Whilst alevaire is of value in aiding expectoration of mucoid sputum, it is not more effective than a control solution containing water only, so that it acts merely by hydrating viscid sputum (Palmer 1957). Opinion has been divided on the value of trypsin. Good results have been reported (Unger and Unger 1953, Harwood Stevenson and Kinnier Wilson 1957), but others have reported side reactions, including dyspnœa, wheezing, fever, hoarseness and nasal and eyelid irritation, and in addition, they have not been impressed by its mucolytic action in vivo (Farber et al. 1954, Forbes and Wise 1957). Chymotrypsin is thought to be less irritant than trypsin and promising results by insufflation of the dry powder into the bronchial tree have been reported (Robinson et al. 1958). However, when chymotrypsin—either as a fine, dry powder, or suspended in an inert propellant—was given daily for periods ranging between a month and six weeks to chronic bronchitics, 15% of patients had wheezing, acute breathlessness, cough, and a big reduction in vital capacity, and therapy had to be discontinued (Leggat 1960). Thus, the mucolytics in present use are either not more effective than a simple water mist, or have undesirable and often serious side-effects. Moreover, trypsin and chymotrypsin are expensive, an important disadvantage in the treatment of a disease as common as bronchitis.

The ideal mucolytic agent, therefore, would reduce the viscosity of mucoid sputum more effectively than a simple water aerosol, and yet be well tolerated and cheap.

There is good evidence that when polysaccharides are exposed to the action of a reducing agent in the presence of molecular oxygen, depolymerisation of the polysaccharide molecule occurs with a striking and rapid reduction in viscosity. This reaction is accelerated by cupric ions (Robertson et al. 1940, 1941, Skanse and Sundblad 1943, Hale 1944). As the sputum mucoprotein complex contains approximately 50% of polysaccharide (Brogan 1959) it was thought possible that this reaction might reduce the viscosity of mucoid sputum. This application to the problem of viscid bronchial secretion has not been previously studied. A tablet containing 100 mg. ascorbic acid, 70 mg. sodium percarbonate, and 0·2 mg. copper sulphate is now available commercially ('Ascoxal', Astrapharm Ltd.). This paper reports experiments to assess its value as a mucolytic agent in chronic bronchitis.

Method

First Experiment

15 patients with chronic bronchitis were studied. They had been in hospital for a few days or weeks, were expectorating mucoid sputum, and were not having any drugs; hence they were considered to be in a stable phase. Patients were studied in the afternoon because the viscosity of sputum is most constant at this time (Palmer 1960). The experiment consisted of three parts: (1) sputum was collected in a dry container until approximately 3 ml. had been produced and its viscosity was measured (see below); (2) one tablet of ascoxal was dissolved in 2 ml. of warm water, the resulting solution being nebulised in a Collinson apparatus by oxygen. In this way a fine "dry" mist is produced with a particle size of 0·5–3·0 μ, which penetrates deep into the bronchial tree. The inhalation was continued until the solution had been completely aerolysed which took about 15 minutes; (3) sputum produced for one hour after the inhalation was collected and its viscosity measured. This procedure was followed once each day for periods varying from 3 to 5 days.

Patients were asked whether expectoration was easier after the inhalation and any change in rhonchi was noted. Viscosity was measured in a cone and plate viscometer which was specially designed for this purpose (Palmer 1957). Viscosity is expressed in degrees of rotation of the cone, the deflection increasing with greater viscosity.

TABLE I—EFFECT OF ASCOXAL SOLUTION IN VITRO ON SPUTUM VISCOSITY

Tube containing	Mean viscosity of sputum (× 10) (degrees of deflection)	Range
Sputum	358·6°	145°–564°
Sputum + water	189·7°	54°–297°
Sputum + ascoxal ..	<5°	0°– 9°

The accompanying figure shows the mean of the daily reduction in sputum viscosity in each patient after the aerosol inhalation of the ascoxal solution. The mean reduction in viscosity for the 15 patients 198·8° (52·7%) (range 125°-340°). All the patients felt that the inhalation had helped them greatly in assisting expectoration—this being especially noticeable after the first two or three inhalations and in cases where the sputum was initially very viscid and a notable reduction in rhonchi was observed.

Further Investigation: In-vitro Tests

Second Experiment

Specimens of mucoid sputum were collected from 10 different patients with chronic bronchitis and put into labelled test-tubes as follows: (1) 4 ml. of sputum; (2) 2 ml. of sputum and 2 ml. of water; (3) 2 ml. of sputum and 2 ml. ascoxal solution. The tubes were incubated for thirty minutes in a water bath at 37°C, and at the end of that time 2 ml. of the mixture was taken and its viscosity measured.

The viscosity of the mixture in the tube containing sputum and water was about half that of sputum alone, but the ascoxal-sputum mixture was reduced to the consistence of water (table I). As this powerful mucolytic effect occurred constantly with each different specimen of sputum, further experiments were undertaken to assess the effect of the time of incubation and the concentration of the ascoxal solution on this reaction.

TABLE II—EFFECT OF CONCENTRATION OF ASCOXAL SOLUTION AND TIME OF INCUBATION ON SPUTUM VISCOSITY

Tube containing	Viscosity of sputum (degrees of deflection)		
	10 min.	20 min.	30 min.
Sputum	182°	193°	175°
Sputum + water	74°	63°	76°
Sputum + ascoxal	<5°	<5°	<5°
Sputum + 1/2-strength ascoxal ..	50°	37°	18°
Sputum + 1/3-strength ascoxal ..	65°	70°	49°
Sputum + 1/4-strength ascoxal ..	78°	75°	68°

Third Experiment

2 ml. of sputum was put into 12 test-tubes and incubated in a water bath at 37°C with 2 ml. of ascoxal solution of varying strengths which was prepared by dissolving 1 tablet of ascoxal in 2, 4, 6, or 8 ml. of water. Three tubes containing sputum and three containing sputum + 2 ml. of water were used as controls. At the end of 10, 20, and 30 minutes' incubation 2 ml. specimens were taken from the test-tubes and the viscosity measured.

Table II shows that ascoxal reduces the viscosity of mucoid sputum rapidly (in ten minutes) but that this effect is much less when the strength of the ascoxal solution is reduced.

Comment

These experiments demonstrate that ascoxal solution is a very effective mucolytic agent both in vitro and in vivo. The mean reduction in sputum viscosity after the aerosol inhalation of 1 tablet dissolved in 2 ml. of water was 52·7%, which compares favourably with that of 21·5% obtained after the inhalation of a water mist for 1 hour (Palmer 1960).

Viscid mucoid sputum incubated with ascoxal solution in vitro is rapidly reduced to the consistence of water. The concentration of ascoxal is important, however, and this rapid mucolytic action is less marked when 1 tablet of ascoxal is dissolved in more than 4 ml. of water. For this reason, in cases where there is a lot of retained sputum or the sputum is extremely viscid, 2 tablets of ascoxal should be dissolved in 4 ml. of water and the concentration of the ascoxal solution should not be less than this. The solution of ascoxal for aerosol inhalation must always be freshly prepared—the tablets dissolve rapidly in warm water giving a pinkish slightly frothy solution. The tablets must be allowed to dissolve completely before aerosol inhalation is started otherwise blockage of the Collinson can occur.

Ascoxal is well tolerated. None of the patients reported any side-effects and it has since been given to a further 23 patients with chronic bronchitis (1–2 tablets in 2–4 ml. water thrice daily for up to a month) without the development of any side-effects.

Ascoxal is cheap: 24 tablets cost 5*s.* + 1*s.* 3*d.* purchase tax; one inhalation therefore costs just over 3*d.* whereas one aerosol inhalation of crystalline trypsin costs 10*s.* 6*d.* (Hospital prices are quoted in each instance.) A larger pack of ascoxal is to be introduced in the near future which will not apparently carry purchase tax.

An effective non-toxic mucolytic agent has many uses. When sputum is viscid, the cough reflex is inactive, or there is respiratory paralysis, sputum is retained in the lungs; under these circumstances it may impede ventilatory efficiency and cause death from asphyxia, occlude a major bronchus and cause massive or lobar collapse, and by interference with ciliary activity in the smaller bronchi give rise to segmental collapse and diffuse bronchopneumonia (*Lancet* 1957). In chronic bronchitis with incipient respiratory failure (i.e., a raised blood pCO_2) the need to overcome sputum retention and thereby improve ventilatory efficiency is urgent, and ascoxal has been given to these cases (often in combination with 1% isoprenaline) with great benefit. It has also been found of much value in the management of viscid bronchial secretion in the patient with severe pulmonary disease in whom a tracheostomy has been performed.

To obtain satisfactory results it is essential that an effective nebuliser be used because the particles of the aerosol mist must be small enough to penetrate the bronchioles. For this reason hand inhalers which give a mist of variable droplet size are not recommended and aerosol inhalation should be by an apparatus such as the Collinson which gives a fine " dry " mist.

Summary

A solution containing ascorbic acid, sodium percarbonate, and copper sulphate (' Ascoxal ') was found to have a powerful mucolytic action when given by aerosol inhalation to 15 chronic bronchitics. In all 15 expectoration was easier after the inhalation, and rhonchi were less; no side-effects were observed. A rapid mucolytic effect was also demonstrated in vitro: the concentration of the ascoxal solution was shown to be important in this effect.

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Preliminary Communications

HEPATIC RETROJECTION

A Technique for Investigating the Local Action of Substances on the Human Liver.

STUDY of the effects of hormones and drugs on the metabolism of the human liver is difficult, because of the inaccessibility of the portal vein and because of the interference from splanchnic and peripheral tissues when substances are given systemically. Studies in animals often involve elaborate preparations with changes in hepatic circulation, or indirect deductions from observations with isotopes; and the results are not always directly applicable to man.

In the lung, wedging of cardiac catheters into terminal vessels has given valuable information, and we have now applied this technique to the liver. Since the venous pressure gradient across the liver is low, we concluded that the flow might be reversed and a segment of liver injected with test substances from a catheter wedged terminally in one of the hepatic veins. This method avoids a direct effect on the splanchnic bed, and since the effective dosage is much less than by the systemic route, the consequences of recirculation might be negligible.

Catheterisation of patients solely for the development

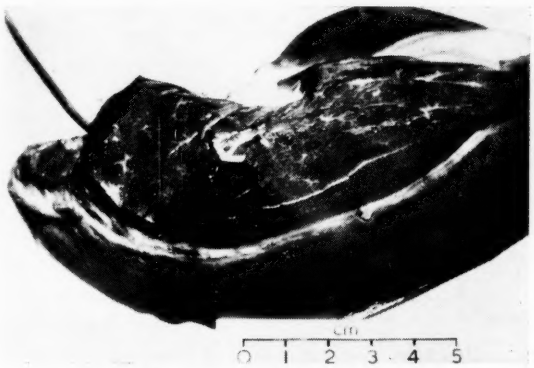

Fig. 1—Liver retrojected with azovan blue dye.

of this technique was not thought to be justified. The studies were performed in fasted patients undergoing routine cardiac catheterisation, who were otherwise fit, with no cardiac failure and no liver disease. Whenever possible, a no. 8 Cournand double-lumen catheter was used, with 3 cm. separating the end and side holes. Its introduction into the liver at the end of cardiac catheterisation usually occupied only a few minutes.

" Hepatic retrojection " is suggested as a name for the technique.

PRELIMINARY STUDIES

When azovan blue (Evans blue dye) was retrojected into human livers at necropsy, it stained roughly conical segments, weighing about 15 g., whose bases often lay on the surface of the liver (fig. 1).

With volumes of dye ranging from 2 to 5 ml. the segments stained were roughly similar; but the most discrete were obtained with 3 ml. Since, for clinical purposes, we need to inject only a restricted segment of liver, and to use adjacent liver for comparison, we have used 3 ml. injections in all our subsequent studies. The test substance is given in 1 ml. of physiological saline or of the patients' heparinised blood, and washed through with a further 2 ml.

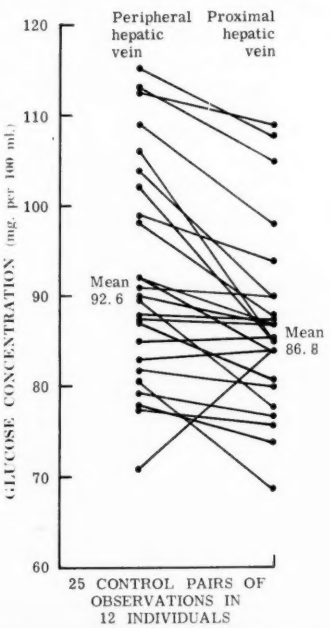

Fig. 2—Simultaneous paired observations on peripheral and more central hepatic-vein glucose levels.

In dogs with intact circulations, hepatic wedging and dye injection (1 ml. azovan blue and 2 ml. physiological saline) stained similar segments. Microscopy showed cellular staining (involving cell membrane, cytoplasm, and nucleus), along the sinusoids and often extending into the portal tracts. Cellular involvement was rather patchy and Kupffer cells were unaffected. No distortion of vascular channels was seen, except in one dog where the sinusoids were dilated but unbroken.

In man, X-ray films following retrojection of 3 ml. sodium diatrizoate (' Hypaque ') defined similar areas. At no time did wedging or retrojection cause discomfort. There was no difference between the levels of serum bilirubin, transaminases, lactic dehydrogenase, and alkaline phosphatase in blood obtained simultaneously from wedge and hepatic vein. Oxygen saturation and total protein content were also similar. Firm injection of 3 ml. saline through the end hole of a wedged catheter produced no change in pressure tracings from a side hole 3 cm. proximal.

From these studies we concluded that drugs could be retrojected into the liver in man from the wedged catheter. Later studies with glucagon showed, in fact, that retrojection occurred even with the catheter free in the hepatic vein; but it is doubtful whether the segment involved is so discrete.

PRESENT TECHNIQUE

To obtain blood samples from the end hole of wedged catheters was always difficult and sometimes impossible. Furthermore, obstruction to blood-flow affects levels of substances handled by the liver, quite apart from any change in metabolic activity. For these reasons, after first wedging, the catheter was slowly withdrawn until equally free delivery of blood was obtained from end and side holes. This always happens after 2 cm. withdrawal, and in this position obstruction to flow was probably not important.

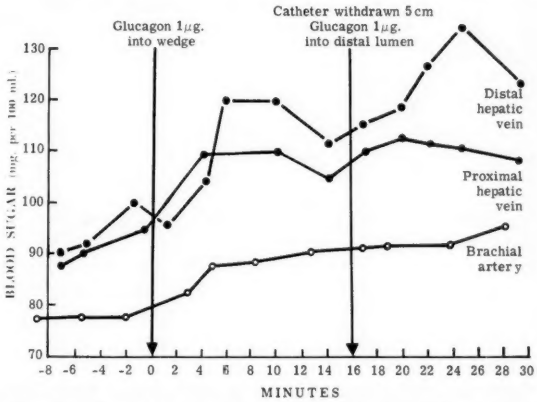

Fig. 3—Results with glucagon 1 μg. (Double-lumen catheter 3 cm.)

With the catheter in this position, synchronous samples were taken from its distal and proximal holes for a control period. It was then rewedged to deliver each test substance, from the end hole, and 15 seconds after retrojection was withdrawn again to the sampling position. Blood was aspirated from the end hole until 1 minute after the injection, to remove as much as possible of the remaining test substance. In an experiment with azovan blue dye, 38% of the injected dose was recovered in this way.

The position of the catheter was checked frequently by fluoroscopy, particularly after any manipulation, to ensure that the sampling position and the wedge injected were unchanged. At each sampling, blood was taken from the brachial artery (and sometimes from a peripheral vein as well), followed immediately by simultaneous samples from proximal and distal hepatic vein.

APPLICATIONS

The effects of glucagon and insulin on the glucose production of the wedge segment are being studied. Glucagon was chosen because its effect on the liver is well known, and insulin because of the controversy about its hepatic action. Because this technique, with direct application to the liver, uses much smaller doses than are usually given, effects on other tissues are very much reduced.

It was thought that greater rise or fall in blood-sugar levels

from the distal as compared to the proximal lumen of the catheter following retrojection would indicate a local effect on the liver segment. On the other hand, equal changes in sugar levels might be the result of widespread hepatic perfusion or of recirculation.

Glucose was measured as diffusible reducing substances on a Technicon Auto Analyser accurate in duplicate estimations to within ±1 mg. per 100 ml.

RESULTS

1. Blood samples from the peripheral part of the hepatic vein showed consistently higher glucose concentrations than those taken simultaneously from the proximal part of the same hepatic vein, whether the catheter was wedged or lying free. The first twenty-five paired control observations in twelve individuals gave a mean difference of 5·8 mg. per 100 ml. (fig. 2), and in only three was the gradient reversed. A progressive rise in glucose concentration along the hepatic vein could be shown by repeated sampling as the catheter was advanced towards the periphery of the liver. These findings suggest that glucose production is greater in peripheral liver tissues than in more central ones. Alternatively, they could result from local variations in blood-flow; which suggests the need for further studies including bromsulphthalein extraction.

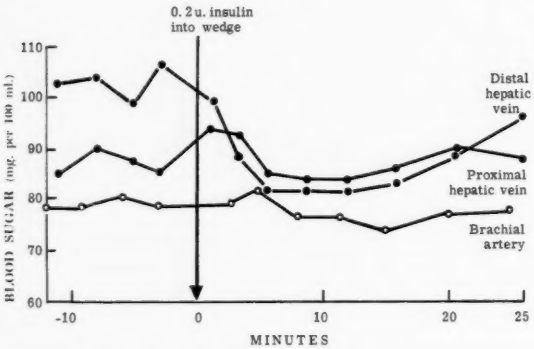

Fig. 4—Results with insulin 0.2 units (9 μg.). (Double-lumen catheter 3 cm.)

Stagnation induced by the tightly wedged catheter could also raise blood-sugar levels. After wedging, delay of 1 minute in sampling raised the sugar level by 8 mg. per 100 ml. This effect was difficult to demonstrate, because of the sampling problems at this site; and it does not explain the other differences in glucose concentration, which were found along the whole length of the hepatic veins. Stagnation was avoided in the retrojection experiments by freeing the catheter as already described.

2. Retrojection of 1 ml. physiological saline washed through with a further 2 ml. physiological saline caused no change in glucose levels.

3. Glucagon (Eli Lilly) given similarly and washed through as above gave a prompt local response with rises of 20–30 mg. per 100 ml. in the glucose levels from the distal catheter. The response was obtained in all of seven trials and was obtained with a dose of only 1 μg. 0·5 μg., given once, produced a smaller but detectable response. The effect could be reproduced in the same segment, and was also obtained with the catheter free in the hepatic vein (fig. 3). It was abolished when the catheter tip was withdrawn into the inferior vena cava for retrojection.

4. With insulin it proved more difficult to show an effect. In the early experiments a single-lumen catheter had to be used, and too big a dose of insulin was initially chosen. As systemic effects were usually apparent, the falls we found in hepatic-vein glucose levels might have resulted in part from a splanchnic insulin effect. The distinction between hepatic and splanchnic effects, using a single-lumen catheter, cannot be made without simultaneous portal-vein glucose levels.

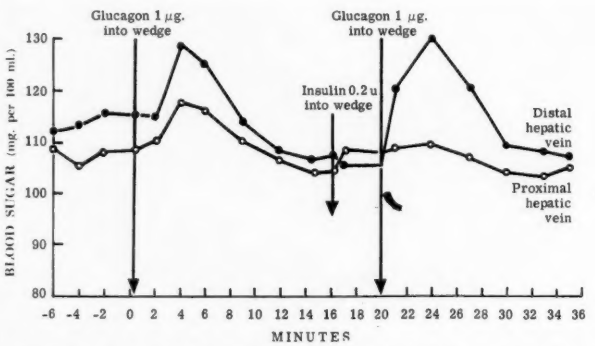
Glucagon 1 μg. into wedge
Glucagon 1 μg. into wedge
Insulin 0.2 u into wedge
BLOOD SUGAR (mg. per 100 ml.)
130
120
110
100
90
80
-6 -4 -2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
MINUTES
Distal hepatic vein
Proximal hepatic vein

Fig. 5—Results with glucagon before and after insulin treatment of hepatic wedge. (Double-lumen catheter 3 cm.)

Using the double-lumen catheter there were only two satisfactory experiments where a suitably small dose (0·2 u., or 9 μg., glucagon-free insulin) was given. In one, changes in both distal and proximal samples were very similar; so a systemic effect, though unlikely, could not be excluded. In the other, however, there was little change in arterial glucose level, and the fall in glucose concentration was greater in the distal samples than in the proximal, indicating that in this patient insulin had a local effect of inhibiting net glucose output (fig. 4).

5. After a control retrojection with glucagon, insulin failed to inhibit the action of glucagon given 3 minutes later to the same segment (fig. 5).

SUMMARY

Hepatic retrojection, a method for studying drug action on the liver, is described. Preliminary studies with insulin and glucagon on glucose metabolism are reported.

We are indebted to Miss B. M. Sargeant for the sugar analyses. Prof. W. J. H. Butterfield gave helpful advice and encouragement throughout. We are grateful to Dr. C. G. Baker and Dr. D. C. Deuchar for permission to make these observations in their patients. J.R.R. was receiving a grant from the British Insulin Manufacturers during this study.

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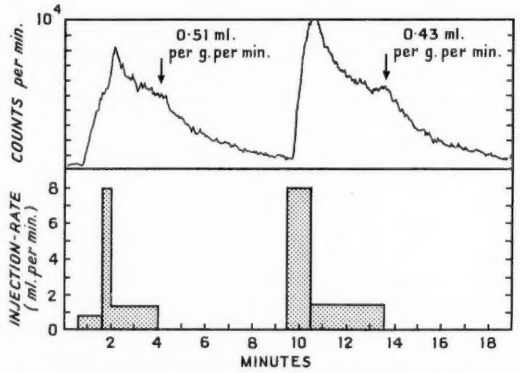
QUANTITATIVE DETERMINATION OF REGIONAL CEREBRAL BLOOD-FLOW IN MAN

Regional disturbance of cerebral function underlies most of the clinically important diseases of the brain. Investigation of such conditions has been severely hampered by the lack of suitable techniques for measuring the regional blood-flow and metabolism within the brain in vivo. The much used inert-gas method [1] permits only a determination of the average blood-flow and oxygen uptake of the brain as a whole, and therefore does not adequately reflect derangements of local cerebral function.

We have recently developed a method for determining regional blood-flow quantitatively and repeatedly within the central nervous system of experimental animals.[2 3] By combining this technique with studies of oxygen and

1. Kety, S. S., Schmidt, C. F. *Amer. J. Physiol.* 1945, **143**, 53.
2. Lassen, N. A., Ingvar, D. H. *Experientia*, 1961, **17**, 42.
3. Lassen, N. A., Ingvar, D. H. *Acta physiol. scand.* (in the press).



Two measurements of regional cortical blood-flow in middle frontal gyrus of right hemisphere in patient undergoing craniotomy for large tumour situated fairly superficially in same hemisphere about 5 cm. posteriorly to measuring site. Measurements were carried out after evacuation of hæmatoma within the tumour. Arrows indicate onset of clearance curves (see text).

carbon-dioxide content in arterial and cortical venous blood, the regional gaseous metabolism of the cerebral cortex in dogs has been investigated.[4 5] We here present our first attempt to apply our method in man. Though the method involves injection of a radioisotope, the radiation doses are much lower than those of other tracer techniques used currently in the clinic.

The inert gas krypton 85, a weak beta-emitter, was dissolved in sterile saline and injected into the right carotid artery of a patient undergoing craniotomy for a large homolateral intracerebral tumour. The patient was anæsthetised with ether and nitrous oxide. The isotope injection was carried out step-wise over $2^1/_2$ to $3^1/_2$ minutes after which the injection was stopped suddenly. The uptake and clearance of the radioisotope was recorded from the surface of the middle frontal gyrus by means of a small shielded Geiger-Müller tube (end-window 6 mm. diameter) mounted about 3 mm. from the cortical surface. The accompanying figure shows two of the five records obtained. The average blood-flow of the superficial cortical layers (about 1 mm. in depth) was calculated to be 0·51 and 0·43 ml. per g. per minute from the two curves shown. This calculation is made from the clearance part of the curves—i.e., the curve obtained after the end of the step-wise injection.

The values obtained are lower than those observed in the frontal cortex of anæsthetised dogs (0·65 ml. per g. per min.).[4 5] This difference is not explained by hyperventilation in our patient (pCO_2 = 36·5 mm. Hg, pH 7·39) since the arterial pCO_2 was also kept between 30 and 40 mm. Hg in the animal experiments. We are inclined to interpret the values obtained as due to functional derangement of the intracerebral tumour, the centre of which was situated about 5 cm. posteriorly to the site of the blood-flow measurements.

The recording of beta radiation by this method demands surgical exposure of the part of the brain in which the *regional* blood-flow is to be determined. This limitation might be overcome by the use of a gamma-emitting inert gas such as krypton 79. The technical advantage of extracranial counting of gamma activity is then obtained at the expense of precision of localisation. It should be emphasised, however, that a craniotomy also makes possible an analysis of locally collected blood samples. The information thus obtained, together with the knowledge of the regional blood-flow rate, allows a systematic investigation of the metabolism of circumscribed parts of the central nervous system *in vivo*.[4]

We are indebted to Dr. Nils Lundberg and Dr. Kaj Nielsen, of the department of neurosurgery, University of Lund, for their great interest and help. The investigation was supported by the Swedish Medical Research Council and Knut and Alice Wallenbergs Stiftelse.

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4. Gleichmann, U., Ingvar, D. H., Lassen, N., Lübbers, D., Siesjö, B., Thews, G. To be published.
5. Gleichmann, U., Ingvar, D. H., Lübbers, D., Siesjö, B., Thews, G. To be published.

Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS AND ASSOCIATION OF CLINICAL BIOCHEMISTS

THE 67th general meeting of the Association of Clinical Pathologists was held in London on Sept. 21–23. The last day was a joint meeting with the Association of Clinical Biochemists. The following are summaries of some of the contributions to the pathologists' meeting:

Fragility of Leucocytes in Leucopenic Disorders

Dr. H. G. H. RICHARDS and Dr. D. L. RICHARDS (Winchester) had estimated leucocyte osmotic fragility in 17 cases of leucopenia, covering a wide variety of causes from toxic to myeloproliferative. In 14 the fragility was much increased, while in 3 it was significantly decreased below normal. These workers suggested that the osmotic fragility of leucocytes is a measure of their average length of life.

Fibrinolysis Related to Age

Dr. H. T. SWAN (Sheffield) reported that estimation of lysis-time in 50% plasma-clot from men aged 21–87, and in surgical or radiotherapy wards had shown that the rate of lysis increased with increasing years. By the method used, the lysis-time at the age of 80 was approximately half that at the age of 40.

Hypoalbuminæmia in Peptic Ulcer

Dr. A. SWAN, Dr. G. T. ALLEN, and Mr. N. C. TANNER recalled that their earlier studies of changes in blood-volume and serum-proteins following cold partial gastrectomy had revealed preoperative hypoalbuminæmia. In a series of cases of chronic peptic ulcer now amounting to 63, they had confirmed a statistically highly significant hypoalbuminæmia, which was especially prominent in terms of total circulating mass. Since there was a tendency to anæmia in the group observed, and since Fauvert et al.[1] had postulated the existence of *anémie protéiprive*, a year or more *after* partial gastrectomy, an attempt had been made to test correlation between Hb and serum-albumin concentration, as well as that between the total circulating red-cell volume and total circulating serum-albumin mass. No such correlation was demonstrated *preoperatively*.

Secretory Pattern of Gastric Mucopolysaccharides

Dr. J. SCHRAGER (Wigan) said that the composition of the gastric mucopolysaccharides being unknown, he had estimated their carbohydrate components. In health, fasting specimens of gastric juice were rich in all the carbohydrate components. With an increase of acid after histamine, the secretion of the carbohydrate components fell. Their secretion recovered within an hour after histamine but fell again with the response

1. Fauvert, R., Hartmann, L., Guenin, P., Thiebauld, L. *Sang*, 1952, **23**, 745.

of pepsin to hypoglycæmia. The gastric mucosa was rich in sulphatase enzymes A and B, which regulated the sulphation of the mucopolysaccharides. There was a constant quantitative relationship between all the carbohydrate components. Patients with duodenal ulcer showed a distinctive secretory pattern. In all specimens the mucopolysaccharide content was very low. In patients with carcinoma of the stomach the quantitative relationship between mucopolysaccharides was disturbed.

Acute Laryngitis and Obstructive Emphysema in Newborn

Dr. G. R. OSBORN and Mr. R. L. FLETT (Derby) said that obstructive atelectasis and obstructive emphysema were frequently found in the lungs of the newborn. Full microscopic examination often revealed the local valvular mechanism responsible. In an important group, however, examination from the trachea to the alveoli failed to disclose the cause. Most, and probably all, of these residual cases were due to acute laryngitis. Laryngitis might develop very soon after birth. Histologically the lesions in the larynx were similar to those associated with indwelling tubes in the œsophagus, trachea, and urethra. In the larynx the lesions were not due to mechanical factors such as intubation, nor were they primarily bacterial in origin. The cause was laryngeal spasm. During this the inferior folds (vocal folds or cords) were damaged by pressure against each other; the superior folds (ventricular bands) might be similarly affected. Spasm was explained by the evolution of the larynx. This organ was not evolved for speech: it was an inlet and outlet valve. Alveoli were not filled with fresh air during inspiration. Their filling depended largely on expiration against the resistance of the contracted bronchial musculature and partly closed larynx. Excessive resistance would produce obstructive emphysema, which might progress to interstitial emphysema and pneumothorax. Complete failure of this resistance at birth could be the cause of the formation of hyaline membrane in the alveolar ducts; whether this was so or not could only be proved by the laryngologist.

* * *

The proceedings of the joint meeting included the following:

Muscle-potassium Assessed by Biopsy

Dr. C. T. G. FLEAR (Cambridge), A. O. CAMPANA, and IRENÉ FLORENCE (Birmingham) submitted that, despite the very considerable variability in composition of human skeletal muscle, biopsy could afford a useful index of cellular potassium throughout the muscle sampled. In view of the negative correlation between sodium and potassium, it was essential, when evaluating the potassium content of a biopsy specimen, to take into account its sodium content. It was also necessary to evaluate the value from a biopsy specimen against normal values obtained from the same skeletal muscle.

Obesity

Mr. G. L. S. PAWAN said that, in the obese, daily calorie intake was sometimes no greater, and might even be less, than in non-obese persons. Total energy expenditure, efficiency of energy utilisation, and the response to calorie reduction might be different from that in normal individuals. Fasting blood levels of non-esterified fatty acids and pyruvic, lactic, and citric acids were higher than normal, and the levels of these responded differently to glucose administration. Normal persons given a 1000-calorie diet, in which 90% of the calories was supplied as fat, exhibited within a few days pronounced hyperketonæmia, hyperketonuria, hypoglycæmia, and negative nitrogen balance. The obese seemed to tolerate this diet better than the non-obese, showed little or no ketosis, maintained blood-sugar within normal levels, and showed little body-protein loss. In the obese there was some evidence of increased use of the pentose-phosphate pathway of carbohydrate metabolism; liver function was often abnormal; and phosphorylase activity of subcutaneous adipose tissue and urinary excretion of certain steroids were higher than in normal persons. It is suggested that in the study of obesity attention should be directed, not only to appetite regulation and calorie intake, but also to energy expenditure and to the metabolic factors influencing synthesis, mobilisation, and utilisation of body-fat stores.

Red-cell Antigens and Enzymes after Storage

Dr. R. G. HUNTSMAN (Peterborough), Dr. B. A. L. HURN, Miss ELIZABETH IKIN, Dr. H. LEHMANN (London), and Dr. J. LIDDELL (Oxford) reported that for serological purposes storage of red cells frozen rapidly in liquid nitrogen was a convenient alternative to preservation of red cells with glycerol. Blood anticoagulated with 1 mg E.D.T.A. per ml. was mixed with half its volume of 40% sucrose.[2] The mixture was added drop by drop to the liquid nitrogen through a fine needle connected either to a syringe or, for larger quantities, to a plastic transfusion bag compressed by weights. The frozen pellets were stored in a Linde liquid-nitrogen refrigerator LNR-25-B. Recovery of intact cells, grouping properties, and four intracellular enzymes were measured after storage at −196°C (liquid nitrogen), −100°C (electrical refrigerator), and −78°C (CO_2 snow). Over a period of two months at −196°C recovery remained at 90–95%, which was the same as that obtained immediately after freezing. There was no deterioration in grouping properties. Aldolase and glutamic oxalacetic transaminase had fallen by 14% and 17% respecively. Glucose-6-phosphate and 6-phosphogluconic-acid-dehydrogenase activities appeared to be enhanced. Present results suggested that storage at −100°C and −78°C was less satisfactory.

Partial Hepatectomy

Dr. H. CLEAVE said that 3 cases of partial hepatectomy performed by Mr. RODNEY SMITH had been studied postoperatively. The estimated bulk of liver tissue recovered was 75% in case 1, 90% in case 2, and 50% in case 3. In case 2 the blood-urea fell from 23 mg. per 100 ml. preoperatively to 9 mg. on the second day, and the prothombin level from 466 mg. per 100 ml. to 266 on the first day, rising to 692 mg. on the ninth day. These findings suggested that the removal of nine-tenths of the liver was near to the limits of tolerance. Of the serum enzymes studied the glutamyl pyruvic transaminase rose rapidly in the first three days in all cases, reverting to normal over a period of up to twenty days. This was assumed to reflect necrosis of some of the residual tissue. The lactic dehydrogenase, on the other hand, rose after operation and remained at a fluctuating high level for two weeks. Experimental studies suggested that this activity might represent the initial stages of liver rejuvenation. Immediately after operation the albumin levels fell, with a corresponding rise in total globulins, and these levels recovered only slowly during the patient's stay in hospital.

In all patients the histological appearances of the residual liver were normal.

Monoamine-oxidase Activity in Toxæmia of Pregnancy

Dr. M. SANDLER, Miss JENNIFER COVENEY, and Miss ELIZABETH BALDOCK had detected small but significant decrease in monoamine-oxidase activity in placentas from patients with toxaemia of pregnancy, compared with placentas from normal pregnant subjects. This change tended to be greater in patients with more severe manifestations of the disease. Although the recovery of 5-hydroxyindoleacetic acid after 5-hydroxytryptamine ingestion was significantly decreased in toxæmia, suggesting a generalised monoamine-oxidase defect, this interpretation was not confirmed when 24-hour excretion of tryptamine was used as an index of enzyme inhibition. There was a significant increase in tryptamine output in normal pregnancy; but, instead of the further increase which might have been predicted in the presence of a generalised enzyme defect, toxæmic patients showed a decrease to non-pregnant levels.

2. Huntsman, R. G., Hurn, B. A. C., Lehmann, H. *Brit. med. J.* 1960, ii, 118.

THE LANCET
LONDON 7 OCTOBER 1961

Latest Thoughts on the Cardia

OUR knowledge of the anatomy and physiology of the œsophagogastric junction region has been greatly extended since modern manometric techniques were first applied by FYKE et al.[1]; and now cinefluorography has enabled the physiologists' ideas to be tested by an independent method. Information needed to define the anti-reflux mechanism is steadily accumulating, and most of the older ideas are being shown to be faulty. There seemed to be grounds for supposing that there is an intrinsic valvular mechanism—in the form of bunching of mucosal folds at the œsophagogastric junction [2–5] or flap valves or the " angle of entry " of the œsophagus into the stomach.[6] But the fact that the lining of a wide tube puckers when the lumen closes is not in itself sufficient reason for attaching a functional importance to such puckering, and the evidence for the muscles needed to close the valves or flaps is not conclusive. Nor have the proponents of these mechanisms explained adequately why they work intermittently in hiatus hernia. By means of cinefluorography, BERRIDGE [4] found that the angle of entry varied too greatly with the position of the subject to be of any consequence in preventing reflux, and he could not demonstrate a flap valve at the cardiac notch.

The discovery in the last few centimetres of the œsophagus of an intrinsic sphincter which relaxed reflexly early in the swallowing process seemed to go a long way towards establishing the mechanism,[1 7] but it was obvious that the tone of the sphincter as measured could not withstand the differences in pressure across the diaphragm that were commonly detected. The tone was usually measured by an open-tube method which recorded the positive squeeze of the muscle-fibres.[8] This component of the contraction of the sphincter was said to be less important than the resistance of the fibres to a distending force; this could be measured only by a miniature balloon, but even this expedient failed to make the sphincter strong enough to prevent reflux.[9] It was then realised that the last 2 cm. of the œsophageal sphincter was normally intra-abdominal, so that any rise of intra-abdominal pressure would press on the walls of the sphincter besides increasing intragastric pressure. The sphincter had therefore to withstand only intrinsic changes in intragastric pressure. In hiatus hernia the abdominal gullet became intrathoracic, was subjected to negative intrapleural pressure, and so could no longer prevent reflux. This supposed mechanism seemed to explain the success claimed for sewing the fundus to the wall of the œsophagus, previously attributed to the angle of entry so formed [6]; but it failed to explain why reflux did not occur during the relaxation of the sphincter when a normal person swallowed, and why reflux could be abolished simply by ensuring that the œsophagus, or a narrow tube fashioned from the stomach, passed through a narrow hiatus.[10 11]

CHEVALIER JACKSON [12] and many later workers believed that the diaphragm had a " pinchcock " action. MILSTEIN [10] has described how the œsophagus passes obliquely through the almost vertical hiatus in a tunnel of diaphragm 3 cm. long, and how half the œsophageal wall must be subject to negative intrathoracic pressure while at the same level intra-abdominal pressure is applied to the opposite wall. He believes, on surgical and anatomical evidence, that in some way the hiatus is the most important factor in controlling reflux, but that there is no " pinchcock " action. The weakness of any hypothesis involving closure of the lumen by contraction of the diaphragm is that such compression as can be recorded by manometry occurs only during inspiration, and even then does not firmly close the lumen.[9] Radiologists on the other hand have seen complete emptying of the transhiatal segment of the gut with inspiration, but the speed of closure (0·125 sec.) was too rapid for contraction of the diaphragm or the intrinsic sphincter.[13] Moreover, this emptied segment of gullet filled only when the pressure built up in the œsophagus by the weight of a bolus, or by a peristaltic wave, was greater than the intragastric pressure.[2 13 14] CREAMER et al.[13] believe that the segment is emptied by the difference in pressure between the abdomen and thorax because the œsophagus behaves like a " flaccid tube, running from a chamber of lower to a chamber of higher pressure ", so that " the part of the tube subjected to higher pressure would collapse as a 'flap valve' and only open to allow forward flow when the pressure gradient has been overcome ".

The mystery of the anti-reflux mechanism has been seemingly solved so many times that new hypotheses may reasonably be regarded with scepticism. But this explanation by CREAMER et al. is perhaps the most promising; and it has been extended by EDWARDS,[9] whose results are based on manometric and radiological findings. EDWARDS found that in some patients with a hiatus hernia barium would not always flow from the intra-abdominal to the intrathoracic stomach, and that in the supine position the pressure inside the intrathoracic loculus of a hernia was not always the same as the intra-abdominal pressure. During a radiological examination a hiatus hernia might therefore be missed if reliance was placed on filling the loculus from the intra-abdominal stomach, although its presence could be demonstrated by swallowing more barium against gravity. EDWARDS suggests that normally the œsophagus

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2. Dornhorst, A. C., Harrison, G. K., Pierce, J. W. *Lancet*, 1954, i, 695.
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4. Berridge, F. R. *Brit. J. Radiol.* 1961, **34**, 487.
5. *Lancet*, 1958, ii, 357, 566.
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10. Milstein, B. B. *ibid.* p. 471.
11. Collis, J. L. *Thorax*, 1951, **12**, 181.
12. Jackson, C. *Laryngoscope*, 1922, **32**, 139.
13. Creamer, B., Harrison, G. K., Pierce, J. W. *Thorax*, 1959, **14**, 132.
14. Fleshler, B., Hendrix, T. R., Kramer, P., Ingelfinger, F. J. *J. appl. Physiol.* 1958, **12**, 339.

behaves as a flaccid compressible tube passing through the hiatal slit, abdominal pressure tending to evert and extrude the tube and its contents into the chest:

" If the walls of the slit approximate the two sides of the tube, the tube will tend to close and, having closed, the greater the difference in pressure between the two compartments the more firmly will the tube be kept closed. An essential feature of the mechanism is that the tube must become closed before the potential eversion or extrusion process can keep the tube closed . . . peristaltic waves empty it and approximate its walls, whilst the intrinsic sphincter tends to keep the walls approximated between swallows."

If the slit mechanism is efficient, the intrinsic sphincter has to withstand only the difference between intragastric and local intra-abdominal pressure. In hiatus hernia, if the hiatal slit is small enough, the mucosal surfaces of the stomach may be adequately opposed, so that effective closure of the lumen can be maintained by intra-abdominal pressure. The flow of gastric contents from intra-abdominal to intrathoracic stomach, and the rate of change of intrathoracic-stomach pressure, is therefore controlled by the slit mechanism. Gastro-œsophageal reflux depends, then, on whether the intrinsic sphincter can withstand the difference in pressure between the intrathoracic stomach and the lower œsophagus—which may explain an earlier observation of a relation between the tone of the sphincter and symptoms of reflux in patients with hiatus hernia.[15]

Even if this hypothesis is correct, there is still much to learn. How are vomiting and belching controlled; what is the cause of the failure of the hiatal mechanism; and why are the symptoms attributed to hiatal hernia and reflux so often intermittent and so often reduced in the obese by weight loss? It seems unlikely that this new concept of the anti-reflux mechanism will influence medical treatment; but in the surgical approach it may increase the emphasis on tailoring the hiatus to a slit and preserving the flexibility and compressibility of the contents of the hiatal tunnel.

Prison Doctors

A CORNER of medical practice—one might almost say a backwater—that receives little attention is the work of doctors caring for people detained in prisons and borstals. Numbering 52 (plus 62 part-timers, mostly general practitioners on call to small places)[16] they are in a sense specialists; prison problems are usually complex and often unique, and ethically the doctor is poised between his professional duty to his patient (whose main purpose may be to deceive him) and his duty to his lay colleagues who may believe him to be in some way " on the prisoner's side ". At the same time the prison doctor is among the most general of practitioners—dealing with diverse disorders under conditions of overcrowding and red-tape, without normal access to hospital facilities, and largely isolated from outside medical colleagues.

The obvious medical specialty for the prison doctor to take up is psychiatry. Whatever one may think of the definition, cause, or treatment of " psychopathic personality ", the abnormal conduct which we call crime falls among the sciences of human behaviour—mainly psychiatry, psychology, and sociology. But the prison medical service has experienced a vicious circle of understaffing, and, whatever good intentions the Prison Commissioners may have had, very few prison doctors have been spared for formal training in any of these special subjects. The Cambridge Institute of Criminology now offers useful short courses for prison doctors, among others; but such courses cannot provide the training in psychiatry needed to enable them either to present an informed psychiatric report to courts or to select those offenders who are most likely to benefit from psychiatric treatment.[17] The service remains understaffed because the terms and conditions of service are unattractive. As in the military services (from which some prison doctors come), the organisation is inevitably somewhat dictatorial. A man is " posted " from place to place, and prison accommodation is not always in a district likely to prove acceptable to the doctor's wife or helpful to his children's education. Promotion, by seniority, is very slow, and salaries are rather lower than N.H.S. equivalents, despite a rise last January. The dissatisfaction of some of those engaged in the service was expressed two years ago in our correspondence columns.[18]

It is especially unfortunate that this important service should be in difficulties at a time of unusual demands on it—and not only because of prison overcrowding. The challenge of the Mental Health Act—especially the provisions for those with " psychopathic personality "—calls for new and careful decisions on whom to transfer and where to send those that are transferred. The law of diminished responsibility for murder (of which few people have made much sense) may well be superseded very soon and fresh problems posed. Prison doctors, we learn, are to be eventually responsible for selecting cases for the psychiatric prison at Grendon Underwood.[19]

Amalgamation of the prison medical service with the N.H.S. would undoubtedly solve many problems. The Ministry Working Party on Special Hospitals [20] rightly called for greater flexibility and freer interchange of staff between the two services, but did not go quite as far as recommending union. Part-time general practitioners already do much of the work quite successfully in smaller establishments and could do more, and outside specialists could be called on more often. But there is some cogency to the objection that doctors employed by outside bodies may lose the confidence (already tenuous enough) of the disciplinary staff. Esprit-de-corps really is important in the prison service; and prison doctors should be enabled to take more, rather than less, part in the team-work which should turn prisons into therapeutic communities. The best hope might be to give the prison medical service

15. Atkinson, M., Edwards, D. A. W., Honour, A. J., Rowlands, E. N. *Lancet*, 1957, ii, 1138.
16. Report of Prison Commissioners for the year 1960; chap. 7, para. 50. H.M. Stationery Office, 1961.
17. See *Lancet*, Sept. 9, 1961, p. 591.
18. *ibid.* 1959, i, 734, 784, 838, 885, 944, 1048, 1100.
19. Stone-laying address by Mr. R. A. Butler. See *Times*, July 2, 1960.
20. Special Hospitals: report of a working party. H.M. Stationery Office, 1961. See *Lancet*, 1961, i, 868.

special status in the Civil Service: its structure would be parallel to that of the N.H.S. with interchangeability between the two services, but it would retain its identity under the Prison Commission. "Posting" within the service is probably unavoidable if a man is to gain experience of different sorts of establishment and make a good principal medical officer; but it should be possible to bring about improvements in other respects and to encourage the flow of recruits. Only by further recruitment can the way be opened to specialism, which is essential.

A careful study of the situation is overdue. The Royal Commission advocated in the Wolfenden report [21] would perhaps be too much of a sledgehammer for this particular nut, which might be cracked by an inter-departmental committee.

Annotations

THE DENTAL STATE OF YOUNG ADULTS

LAST week those attending the 40th anniversary celebrations of the Royal Army Dental Corps were able to study the results of an inquiry by Capt. A. M. Milne into the dental state of 875 National Service men, newly recruited to the Army. Although the survey was originally designed to supply information relevant to investigations into the ætiology of caries and pyorrhœa, Milne's findings seem to bear closely on the whole question of treatment in the General Dental Service.

The recruits investigated may be taken as a rough cross-section of the young men between 18 and 22 in this country; and even a cursory examination of the findings brings to light a disturbing state of affairs: already 25% of their teeth had been destroyed by dental caries. Although they had, at that age, passed through the period of greatest caries incidence (generally believed to be childhood and adolescence), there can be no doubt that in the absence of adequate treatment still more teeth would be lost from the slow progression of lesions already present, since 9 out of 10 of the recruits still had active caries. Indeed an average requirement of one further extraction per man remained to be carried out; and by the time treatment has been completed, 1 man in 4 will be wearing a denture.

Disquieting as these findings are, they were not entirely unexpected. What was more surprising and even more disturbing was the state of the supporting tissues of the teeth. It had been thought, until recently, that periodontal breakdown—that is, the gradual destruction, by chronic septic ulceration, of the supporting tissues of the teeth—was essentially a disease of adult life. It has recently been shown,[22] however, that its cause is related to the morphological pattern of tooth eruption and to incidental trauma connected with it, and that therefore this disease also begins in adolescence. The Army findings support that hypothesis, for it was found that half the men already had pyorrhœa pockets, extending below the anatomical necks of the teeth, and that more than 4 out of 5 of them had active ulceration in the subgingival crevice—a condition which, unless treated, leads to the eventual destruction of the supporting bone and fibrous attachment of the tooth.

These observations are particularly significant because, though the treatment of caries is widely practised and is readily available to most of those sensible enough to apply for it, very little treamtent of periodontal disease, beyond routine scaling, seems to be undertaken. The difficulty is, at least in part, administrative; for while a case can be made out either for or against payment by an itemised scale of fees for the filling of teeth, it is hard to see such a system working for the treatment of periodontal disease. Yet effective means of treatment have been taught in most dental schools for some years, and the problem must be tackled.

Methods of prevention have not been so well explored as treatment. Indeed the precise details of the ætiology of the disease and the technique of preventive procedures are only now being worked out; but Milne's review indicates that work in both these subjects is on the right lines, and it should not be long before reliable measures are established for halting the destructive processes in adolescence, thereby preventing serious damage to the supporting structures of the teeth.

Unfortunately, research into the precise cause of caries has not yet given so promising a lead. Milne's analysis of the habits of a group of caries-free recruits, carried out in cooperation with Prof. Geoffrey Slack, indicates that the factors which have hitherto been regarded as contributory causes of caries do not in fact seem to establish any consistent pattern. The wide acceptance of a hypothesis propounded by Miller 70 years ago, incriminating carbohydrate fermentation, may have misled many investigators, though Miller himself realised that this explanation would not by any means fit all the observed facts. But it is encouraging to know that these discrepancies are now recognised and that statistics are being collected which will permit a more accurate assessment of the factors involved. In particular, the news that the Medical Research Council have established a unit at Bristol to investigate the ætiology of caries is very welcome.

THE DISPLACED EYE

WHEN a patient has sustained concussion, multiple fractures, or other damage dangerous to life, deformity of the facial bones, or possible change in orbital contour, is naturally apt to be disregarded in the first day or so. What is not so immediately understandable is that it is also liable to be disregarded in the first few weeks, the first few months, or even the first year. In the very early stages deformity should be sought by palpation and X-rays, and should be corrected as soon as possible.[1] It is seldom that this cannot be done either under local anæsthesia or under general anæsthesia for that alone or for some other purpose. (A very ill patient may be safer under a modern general anæsthetic in skilled hands than lying quietly in bed unattended.) The deformity cannot always be corrected, and then closed manipulations must give way to open repositioning. So rapid is the healing of facial bones that disimpaction is increasingly difficult after about five days, but McIndoe [2] considered that it was still possible up to the end of the third month. Thereafter shape can be restored to defects only by grafts

21. Report of the Departmental Committee on Homosexual Offences and Prostitution. Cmnd. 247. H.M. Stationery Office, 1957.
22. Cohen, B. *Brit. dent. J.* 1959, **107**, 31.

1. Duke-Elder, S. Textbook of Ophthalmology; vol. 6. London, 1954.
2. McIndoe, A. H. *Brit. dent. J.* 1941, **71**, 235.

of bone, cartilage, fascia, or foreign materials such as plastic resins or glass-wool.

If the deformity involves the orbit of the eye, the principal disability is not abnormality of contour but diplopia. Lyle [3] claimed that this could be corrected by operation on the external ocular muscles, and later [4] analysed in 18 cases the kind of fracture that had led to displacement of the eye, the extent and type of diplopia, the operations required, and the results. Unilateral fracture of the malar bone and maxilla led to downward displacement of the eye, simple or complex deviation of the axis, and defective movement of elevation. Correction could usually be achieved by resection of the ipsilateral superior rectus; but occasionally the ipsilateral superior rectus or inferior oblique had to be weakened, the aim being to secure ocular movements which were symmetrical in all directions. Where the frontal bone was also fractured there might be in addition defective depression and horizontal movement. Multiple procedures were usually necessary, four or five being common. Occasionally fracture of the malar bone and maxilla caused elevation of the eye with defective depression. Resection of the ipsilateral inferior rectus might have to be supplemented by recession of other muscles.

A central nasomaxillary fracture led to depression of the root of the nose, and increase of the interpupillary distance with exotropia. Since the inferior oblique is a stronger muscle than the superior oblique the visual axes were rotated. Simple recession of the lateral rectus might correct all the abnormalities of gaze, but if the excyclotropia was severe other rectus muscles had to be operated on. In every case binocular single vision was achieved, but sometimes at the cost of multiple operations.

ANATOMICAL NOMENCLATURE

THE further revision, six years ago, of the anatomical nomenclature may have aroused in some a wish that instead another step could have been taken towards revitalising medical science's oldest branch in order to bring it into line with the needs of clinical practice. Yet we have cause to be grateful to those who undertook this revision.

The first attempt, in 1895, to produce a standard terminology was made by a group consisting mainly of German anatomists. It resulted in the Basle Nomina Anatomica (B.N.A.), which was never adopted internationally. Revised and improved versions by British anatomists in Birmingham in 1933 (B.R.) and German anatomists in Jena in 1936 (J.N.A.) fared no better.

The present Nomina Anatomica, accepted in principle at the International Congress of Anatomy in Paris in 1955 (P.N.A.) and now issued in a second edition,[5] resulted from a fruitful attempt by an international anatomical nomenclature committee to produce terms which can be accepted by all, in their latin form for international publications and meetings, or in the vernacular equivalent for purely national needs. The success of this committee's efforts is reflected in the general international acceptance of its proposals.

The new terminology is not very different from the one used by English-speaking anatomists for the past three decades. The few divergencies are accounted for mainly by the addition of new terms and the removal of inaccurate ones and of eponyms. Eponyms seem likely to disappear since they are often incorrect, they vary from country to country, and sometimes they commemorate relatively unimportant figures while the names of really great ones are not perpetuated in this way.

3. Lyle, T. K. *Trans. ophthal. Soc. U.K.* 1941, **61**, 189.
4. Lyle, T. K. *Brit. J. Ophthal.* 1961. **45**, 341.
6. Nomina Anatomica 1961. Amsterdam and London: Excerpta Medica Foundation. Pp. 100.

TULARÆMIA

ORGANISMS of the pasteurella group are non-motile aerobic gram-negative rods. They cause various severe infections in animals and two of them—*Pasteurella pestis* and *P. tularensis*—are transmissible to man, causing plague and tularæmia. Rabbits and hares have proved to be a reservoir of infection from which *P. tularensis* is occasionally transmitted to man by the bite of infected fleas or ticks, by handling infected animals, by inhaling their infected discharges, or by ingesting contaminated food and water. Infection contracted in any of these ways leads to various clinical pictures—including cutaneous, pleuropulmonary, oropharyngeal, abdominal, meningeal, and septicæmic tularæmia. It is difficult to estimate the frequency of tularæmia in this country, where the disease is rarely considered in the differential diagnosis of even obscure infections and so laboratory confirmation is rarely sought. More precise investigation of upper-respiratory-tract infections or slowly healing skin sores in agricultural workers, particularly those handling rabbits and hares, might disclose tularæmia as an occupational hazard, much in the same way as it is found in laboratory workers handling the organism.

Overholt et al.[1] have analysed the clinical features, diagnosis, and treatment of 42 cases of tularæmia in laboratory workers, all but 1 of whom had previously received a *P. tularensis* vaccine. The commonest presenting features were those of a febrile constitutional upset resembling influenza or of a respiratory-tract infection with coryza, sore throat, cough, and pleurisy. 20 patients had abnormal chest radiographs with the appearances of pneumonia in 17, unilateral hilar lymphadenopathy in 9, pleural effusion in 5, and perihilar streaking in 1. Because these signs, somewhat resembling those of primary atypical pneumonia, are non-specific, laboratory confirmation is necessary; and this was accomplished by isolating the organism, by serum-agglutination tests, and by a skin test. *P. tularensis* was regularly isolated by guineapig inoculation or culture on glucose-cystine agar from sputum, gastric, or pharyngeal washings, and also rarely from bronchial aspirate, nasal swabs, or blood. In most of those tested, the specific serum-agglutinin titre increased fourfold in the course of five weeks from the onset of the illness. This titre was of value for confirmation rather than for early diagnosis; a fourfold rise in titre was evident in a tenth of patients in the first fortnight, in about a third in three weeks, in three-fifths by the end of a month, and in just under nine-tenths five weeks after the onset. There was no diagnostic fourfold rise in titre in 5 of the 34 patients tested. Serological hæmagglutination tests, using *P. tularensis* polysaccharide, apparently reveal significant rises in titre about a week before bacterial agglutination tests in both vaccinated and unvaccinated patients.[2]

The tularæmia skin test reveals delayed-type or tuberculin-type hypersensitivity; Overholt et al.[1] regarded

1. Overholt, E. L., Tigertt, W. D., Kadull, P. J., Ward, M. K., Charkes, N. D., Rene, R. M., Salzman, T. E., Stephens, M. *Amer. J. Med.* 1961, **30**, 785.
2. Saslaw, S., Carhart, S. *Amer. J. med. Sci.* 1961, **241**, 689.

the reaction as positive if erythema and œdema 10 mm. or more in diameter developed forty-eight hours after the intradermal inoculation of 0·1 ml. of a phenolised vaccine diluted 1 : 1000 with physiological saline solution. Skin tests were performed during the illness in 31 cases: in 17 the test was positive initially, and in the remaining 14 it became positive in the first fortnight of illness.

Like the other pasteurella infections, *P. tularensis* is sensitive to sulphadiazine, streptomycin, the tetracyclines, and chloramphenicol. The present drug of choice is the bactericidal one,[1–3] streptomycin, for treatment with the bacteriostatic drugs is liable to be followed by relapse. In the series of Overholt et al., a third of those treated with tetracycline or chloramphenicol relapsed where treatment was given as early as the first week of illness, but none relapsed where it was instituted after the first week. It seemed that the broad-spectrum antibiotics controlled the infection but did not eradicate the organism from the host. Relapses have not been reported after streptomycin therapy, but unfortunately streptomycin-resistant organisms are commonly encountered in laboratory-acquired tularæmia, as might be expected in those exposed to an environment containing both the organism and streptomycin. Because it induces rapid emergence of highly resistant organisms, streptomycin falls short of the ideal antibiotic for this and other pasteurella infections. Possibly the new penicillin, (' Penbritin '), may prove to be the antibiotic of choice. Preliminary microbiological studies [4] indicate that this has a tetracycline-like activity against gram-negative bacilli, combined with high bactericidal power, and the pattern of drug resistance is of the gentle stepwise type associated with all the penicillins.

FACT AND FICTION IN INFANT REARING

THOUGH mothering is increasingly regarded as a process of the utmost importance, little is known about it. To a large extent the doctor, the midwife, and the health visitor are taking over the authoritative role that has traditionally belonged to the maternal grandmother, whose authority has been weakened by geographical dispersion and social change. Thus the " experts " are now to the forefront in matters of child care. But who, in fact, are these experts? It may be the family doctor, but most medical students are taught hardly anything about child care. Most doctors learn about it from practical experience backed by sound medical training. The expert may be a pædiatrician, whose experience will have been largely with sick children. If he is a psychologist, his knowledge may be theoretical or his experience based on problem children. A social worker may see only problem children or problem families, or may not have the necessary background of training. It is hardly surprising that the " experts " always seem to disagree. Little is known for certain about what mothers actually do with, to, and for their babies—information essential for anyone formulating ideas on child care.

Dr. John and Dr. Elizabeth Newson, of the department of psychology, University of Nottingham, have been trying to find out precisely how ordinary mothers handle their babies, as opposed to how they are advised to. What do they do at bedtime, for instance—do they rock the baby to sleep at a year, or do they just put him down and leave him? If he will not go to sleep, do they cuddle him, feed him, get him up again, let him cry it out, or smack him? Do they respond to the one-year-old's crying, and how quickly? Do they try to stop him getting dirty or playing with his genitals? Do they punish him at this age—and, if so, how and what for?

The survey was carried out on a representative sample of mothers of one-year-old children in Nottingham. More than 700 mothers of one-year-old children were picked at random from the records of the health department, and were interviewed within a fortnight of the child's first birthday. At this year's annual meeting of the British Association the Newsons gave a preliminary report in which they said:

" The truth is, of course, that in the present state of knowledge there is not a sufficient body of well-substantiated evidence on which to base sound practical advice to parents. In fact, when one considers the enormous potential importance of the subject, the amount of research being devoted to the effects of different child rearing practices is quite ridiculously inadequate. It is not only that so few of the theories of child rearing have been subjected to the inconvenience of being reconciled with empirical observation; a good deal of theorising seems to be concerned with a view of child upbringing which is quite out of touch with the way the majority of mothers feel and behave in contemporary society."

It is sometimes said that the prevalence and duration of breast-feeding have declined notably; and the survey suggests that this is true. More than half of all the mothers had given up breast-feeding by the end of the first month; and only about 12% were still breast-feeding at six months. There was no suggestion that this was due to a desire to return to work: in fact, by the time the child was twelve months old, less than 2% of the mothers were back in full-time work, and there was no difference between the occupational classes. Only 8% of the mothers even had part-time jobs, and most of these involved either " outwork " in the home or a few hours' work in the evening.

What was clear was that the mothers were receiving advice that was at variance with what they were actually doing. Because of this the mother was likely to feel a certain amount of guilt at denying her baby what, in magazine articles for women, is often called " his birthright "; and this was reflected in the excuses given for having discontinued breast-feeding.

One question was whether the mother had fed the baby on a rigid schedule according to the clock, or simply when he cried for food. The answers, classified on a four-point scale, were as follows: demand feeding 53%, flexible feeding 22%, flexibly rigid feeding 19%, rigid feeding 6%. There was no appreciable difference between middle-class and working-class mothers, but the ways in which they arrived at their behaviour did appear to differ. In general, working-class mothers tended to feed on demand, often in defiance of medical advice, because it was kinder or because it was easier; middle-class mothers tended to be far more self-conscious, and were inclined to justify their methods as the result of careful consideration of the different schools of thought.

Much attention has been paid in recent years to weaning, probably largely because of the widespread influence of psychoanalytic theory, according to which weaning is a potentially traumatic experience. It is often assumed that the baby will be drinking exclusively from a cup by ten months at the latest, but this was not at all the usual pattern revealed by the survey. At the age of twelve months about 70% of the babies were still using the bottle

3. Saslaw, S., Eigelsbach, H. T., Wilson, H. E., Prior, J. A., Carhart, S. *Arch. intern. Med.* 1961, **107**, 689.
4. Rolinson, G. N., Stevens, S. *Brit. med. J.* July 22, 1961, p. 191.

regularly at least once in twenty-four hours. Although most of the babies were to some extent sharing in the meals provided for the rest of the family, the bottle was still being used largely as a convenient receptacle to drink from. In many homes it was available all day, and the child simply reached for it when thirsty. "The main point that emerges from these findings is that weaning to a diet consisting predominantly of solid foods is normally being accomplished without the baby being asked to relinquish the pleasures of sucking: in this sense the concept of weaning as traditionally understood has become an anachronism." At least 70% of the babies had had a dummy at some time in the first year, and 50% of them were still using one at twelve months. "For the majority of children, then, the psychologists' emphasis on weaning as a traumatic experience seems to be misplaced in view of the extension well into the second year of oral gratification by sucking."

The full results of the survey, to be published in a book, should be of considerable interest to all who work with mothers and children.

ANTIBODIES TO PLACENTA

THE rejection of skin grafts between animals of the same species indicates how differences in tissue antigens, which are genetically determined, may lead to brisk immunological reactions. Both human [1] and animal parents usually reject skin grafts from their children, and maternal reaction to fœtal red-cell antigens in erythroblastosis fœtalis and the formation of antibodies against fœtal white cells [2] are well known. Until recently the existence of maternal antibodies against the fœtal part of the placenta was in doubt.[3] Hulka et al.[4] argued that antibodies might be absorbed in vivo by the placenta, and sought antibodies against the patient's own placenta in serum taken four days post partum. Tube and gel precipitation tests were negative, and the tanned-cell hæmagglutination test was equivocal. The fluorescent-antibody technique, however, revealed definite specific staining of the cytoplasm of the syncytiotrophoblast in all five patients studied.

The antigenic stimulus for the formation of these antibodies presumably arises from the fœtal part of the placenta—the syncytiotrophoblast, which is in direct contact with the maternal blood-stream. Schmorl originally observed trophoblast emboli in the lungs of patients who had died of eclampsia, and Douglas et al.[5] have demonstrated trophoblastic cells in the veins of the broad ligament and the inferior vena cava during pregnancy.

The presence of antibodies does not necessarily denote immunologically determined disease. Antibodies against heart in man [6] and against liver in rats [7] may be regarded as a result, rather than a cause, of tissue damage. When antibodies are potentially pathogenic, their pathogenicity is influenced by the access of antibody to antigen. This is illustrated by the ability of infective virus to increase in amount inside cells which are bathed in viricidal antibody.[8] Some antibodies are macroglobulins, and enter the extravascular space more slowly than the low-molecular-weight γ-globulins and are unable to pass the placenta in more than small amounts.[9] This factor may limit the effect of macroglobulin antibodies on the fœtus.

Bardawil and Toy [10] have discussed the role of immunological reactions to placenta in the diseases of pregnancy. The concept of pre-eclamptic toxæmia as an immunological disease goes back to the beginning of the century, but there is neither an adequate animal model nor collateral evidence in humans. The level of γ-globulin, which is an index of antibody protein, is only occasionally raised in pre-eclamptic toxæmia [11 12]; and complement, which is low in diseases such as acute nephritis and systemic lupus erythematosus where immunological mechanisms are suspected, is only slightly lowered.[13] The association of pre-eclamptic toxæmia with the first pregnancy is not easy to explain on an immunological basis. Degeneration of the syncytial layer of the placenta, fibrin deposition, endarteritis, and infarction are found after the seventh month of pregnancy. The role of immunological mechanisms is unknown.

The method of Hulka et al.[4] for detecting antibodies against placenta, although only semiquantitative, will stimulate interest in these problems and aid their solution.

THE "MEDICAL PRESS"

WITH great regret we record that, with its issue of Sept. 27, our contemporary the *Medical Press* has ceased publication. Founded 122 years ago by Dr. A. H. Jacob as the *Dublin Medical Press*, and combining in 1866 with the London *Medical Circular*, it has always been a journal primarily for the general practitioner; and its early years had the same controversial quality as our own, with the same emphasis on practical reform.[14] Few can now remember any of its 62 years under the editorial control of Arthur Jacob and his son Archibald, who died in 1901; but the family connection has continued through the publishers, Messrs. Baillière, Tindall, & Cox, for the chairman, Mr. R. F. West, and the two other members of the board are all descendants of Archibald Jacob. After the printing was transferred to London in the early years of this century, the *Medical Press and Circular*, as it was still called, gradually became more of a London than a Dublin journal; but until 1936 it had Prof. R. J. Rowlette as its Irish editor, and gained much by reflecting opinion in both countries. In England the editor from 1903 to 1915 was Dr. David Walsh, an English pioneer of radiology. During the next three years Dr. Leonard Williams, of *Minor Maladies*, gave it the flavour of his unit, and from 1918 to 1933 it was very much the journal of Dr. Harry Campbell, whose philosophical reflections each week were an unusual and attractive contribution to medical journalism. Since Sir Cecil Wakeley became chief editor in 1933, the journal has more than maintained its attractiveness for the reader; and the editorials of Dr. G. E. Breen, Dr. J. D. Kershaw, and others have had a force and skill that is perhaps fully appreciated only in other editorial offices. In its final leader, on the aged in hospital, the journal shows the same preoccupation with reform as it showed in its early days in Dublin: the time has come, it says, when we should turn our attention from the captains of the men of death to their subordinates. That a journal so much alive should succumb to increasing costs is no less than tragic.

1. Peer, L. A. *Transplant. Bull.* 1957, **4**, 109.
2. Hitzig, W. H., Gitzelmann, R. *Vox Sang.* 1959, **4**, 445.
3. Wagner, V., Zavazal, V., Kasalova, D., Maly, V., Mecl, A., Prokop, J. *Experientia*, 1959, **15**, 24.
4. Hulka, J. F., Hsu, K. C., Beiser, S. M. *Nature, Lond.* 1961, **191**, 510.
5. Douglas, G. W., Thomas, L., Carr, M., Cullen, N. M., Morris, R. *Amer. J. Obstet. Gynec.* 1959, **78**, 960.
6. Ehrenfeld, E. N., Gery, I, Davies, A. M. *Lancet*, 1961, i, 1138.
7. Weir, D. M. *ibid.* p. 1147.
8. See Burnet, F. M. Principles of Animal Virology; p. 269. London, 1960.
9. Franklin, E. C., Kunkel, H. G. *J. Lab. clin. Med.* 1958, **52**, 724.
10. Bardawil, W. A., Toy, B. L. *Ann. N.Y. Acad. Sci.* 1959, **80**, 197.
11. MacGillivray, I., Tovey, J. E. *J. Obstet. Gynæc. Brit. Emp.* 1957, **64**, 361.
12. Novell, H. A., de Haan, Q. C. *Obstet. Gynec.* 1958, **12**, 154.
13. Vescovo, R. *Ann. Ostet. Ginec.* 1957, **79**, 286.
14. Rowlette, R. J. *The Medical Press and Circular* 1839-1939. London, 1939

Special Articles

"APPENDICITIS" IN YOUNG WOMEN

An Opportunity for Collaborative Clinical Research in the National Health Service

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IT is well known that in young women the diagnosis of appendicitis presents special difficulties, and in many of those operated on no convincing evidence of disease is found (Morrison 1910, Patton 1952, Moir 1954, Samuelsson 1957). An attempt has been made to estimate how common such cases are. The development of the National Health Service and of the statistical services associated with it has provided fuller information on this kind of question, and also gives new opportunities for investigation.

DATA AND METHODS

Since 1949 the General Register Office and the Ministry of Health have been collecting details, through their Hospital Inpatient Inquiry, of patients discharged from N.H.S. hospitals. The material for 1956 and 1957 has recently been published (G.R.O. 1961). In 1956 the inquiry covered 67% of the non-teaching hospital beds, and in 1957 it covered 81%; the percentages of the teaching-hospital beds were higher. The hospitals included formed a very large sample of all those in the country. Each hospital contributed details of every tenth discharge, giving an effectively random sample of its patients. The data from each of the two years give similar pictures, and they have been amalgamated in the present study. Data from earlier years have also been used where specified in the tables.

Besides the age and sex of the patients, the type of admission—whether "immediate" or "other"—was recorded. The cases stated by the hospital to be complicated by peritonitis are shown separately. Cases where the appendix was removed in the course of surgery for other conditions have not been included. The data were originally tabulated in five-year age-groups. As the number of cases was large, the G.R.O. kindly re-analysed the data by single years of age.* In this way a more detailed picture of the effect of age on the number of cases is obtained.

* It is understood that copies of these tables are available from the General Register Office for a small fee.

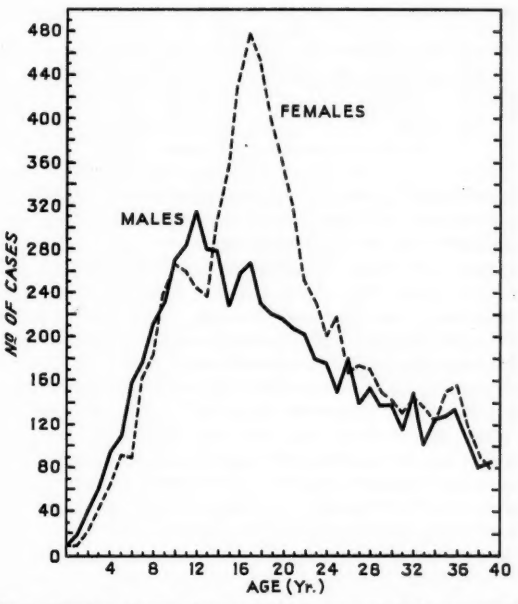

Fig. 1—Number of cases of appendicitis by sex and single years to the age of 40.

The figures are derived from the 18,000 cases of appendicitis at all ages reported to the hospital inpatient inquiry, 1956–57, and they are corrected for variations in the population at risk owing to the "bulge" of postwar births. (The data of figs. 2 and 3 and table I are similar.)

RESULTS

In males the number of cases treated in hospital for appendicitis is highest at the age of 12 (fig. 1). This peak is followed by a fairly steady decline. In females the total number of cases of hospital-treated "appendicitis" follows a different course. There is a minor peak at the age of 10, which is found in the data for 1953–55 as well as those for 1956–57, and which appears to correspond to the male peak at 12. This is followed by a much larger peak at 17. By the mid-20s the number of cases in females is again similar to that in males of the same age.

The great majority of the male cases of appendicitis are admitted "immediately". The male cases not admitted in this way are most common at the age of 12, and numbers then decline slowly (fig. 2). In contrast, the non-"immediate" cases in females form a greater proportion of the total and are most common between the ages of 14 and 26. As a result, the extra cases called "appendicitis" in young women above what might be expected are made up of "immediate" and non-"immediate" cases in about equal numbers.

In both males and females the number of cases of appendicitis reported as being complicated by peritonitis is high in childhood and declines to a minimum in the late 20s and early 30s (table I). In the general population death-rate from appendicitis follows a

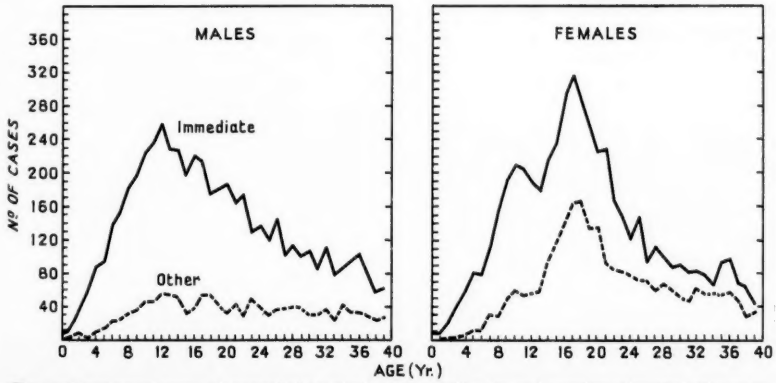

Fig. 2—Number of cases of appendicitis admitted immediately, and number admitted otherwise, by single years to the age of 40.

TABLE I—NUMBER OF CASES OF APPENDICITIS WITH PERITONITIS BY SEX AND AGE *

Age	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39
Male ..	50	72	77	57	49	49	42	49
Female ..	33	66	53	33	30	26	37	34

* National Hospital Inpatient Inquiry 1956–57.

similar trend (table II). Thus neither of these indices of inflammation of the vermiform appendix shows any increase or excess in young women.

Data have been collected by the Hospital Inpatient Inquiry since 1949. Each year the number of hospitals contributing has increased. Because of this change in the size of the sample, simple comparisons from year to year of the numbers of cases reported of a particular condition cannot readily be made. But the excess of female over male cases in the ten-year age-group 15–24 has remained remarkably constant, suggesting that there is no tendency for this rate of hospital treatment for " appendicitis " in females to diminish (table III). Further, it is similar in the most recent data to what it was in the early 1930s (Young and Russell 1939).

All the cases being considered had " appendicitis " as their principal diagnosis when they left hospital. In the age-group 15–24 in 1956 (the only year for which figures

TABLE II—DEATH-RATES PER MILLION PER ANNUM FROM APPENDICITIS BY SEX AND AGE *

Age	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39
Male ..	12	10	11	10	8	9	8	9
Female ..	7	7	6	6	3	4	5	4

* England and Wales, 1954–58.

TABLE III—RATIO OF FEMALE TO MALE CASES OF APPENDICITIS AT AGE 15–24

	1931–35*	1949†	1951	1953–54	1955	1956	1957
Female cases per male	1·8	1·7	1·6	1·7	1·8	1·7	1·6

* Young and Russell (1939). † National Hospital Inpatient Inquiry, 1949–57.

are available) 94% of the female cases with this diagnosis were treated by appendicectomy, and 93% of the male. The duration of stay was similar in males and females, the average being about nine days.

The marital status of the female cases was recorded, and it is possible to calculate approximate age-specific hospital admission-rates for " appendicitis " for the married and the single (table IV). The rate in the single is greater than in the married, but in both married and single it declines rapidly in the 20s. No information on fertility was collected.†

DISCUSSION

The epidemiological method used here can contribute in various ways to the solution of a problem. It can help to clarify and to define its extent, and it can put individual clinical experience in a community perspective. It can remind doctors of problems that have grown familiar, and it may be able to point the way to their solution or at least to ways in which they can be tackled (Morris 1957).

The excess in the number of reported female cases of appendicitis between the ages of 14 and 26 over what might reasonably be expected is at least 7500 in N.H.S. hospitals each year in England and Wales—enough to fully occupy a 200-bed hospital. Since the beginning of the N.H.S. some 100,000 of these *extra* cases called "appendicitis " have been operated on in England and Wales. The chance that a girl of 17 will be operated on for appendicitis is twice what it is for a girl of 13; for males of the same ages the chances are approximately the same. There is no evidence that the number of these cases is declining as the years pass (table III). Thus the introduction of sulphonamides and antibiotics, and all the other developments in therapeutics and diagnosis, have not materially affected the problem. The excess of these cases is as great in the teaching as in the non-teaching

† The fertility of women *dying* of appendicitis is similar to that of women dying from all causes (G.R.O. 1958).

TABLE IV—ESTIMATED HOSPITAL INPATIENT DISCHARGE-RATE * PER 1000 PER ANNUM FOR APPENDICITIS IN SINGLE AND MARRIED WOMEN BY AGE

Age	15–	20–	25–29
Single	8·4	6·8	3·9
Married	5·6	4·1	3·3

* Calculated by scaling up the reported cases (using the factors given by the G.R.O. for teaching and non-teaching hospitals), and expressing these estimated numbers for the country as a whole as rates in the population at risk. England and Wales, 1956–57.

hospitals (fig. 3). A similar excess of " appendicitis " in young women is found in other British data (e.g., War Office 1948, Ministry of Pensions and National Insurance 1958, G.R.O. 1959, Air Ministry 1961). It is also found in American series (e.g., Eisele et al. 1956, Collins et al. 1956, National Health Survey, United States 1959).

These cases have been discharged with a diagnosis of " appendicitis " after undergoing appendicectomy, but no information is available about the histological findings. There seems to be no British series large enough to be divided into age and sex groups, in which the criterion for inclusion has been histological evidence of disease; but in two large American series where this was done no excess in young women was found (Green and Watkins 1946, Eisele et al. 1956). This is in agreement with data from the two indices of real appendicitis that we have for England and Wales—the cases complicated by peritonitis, and the fatal cases (tables I and II).

These extra cases labelled " appendicitis " that occur in

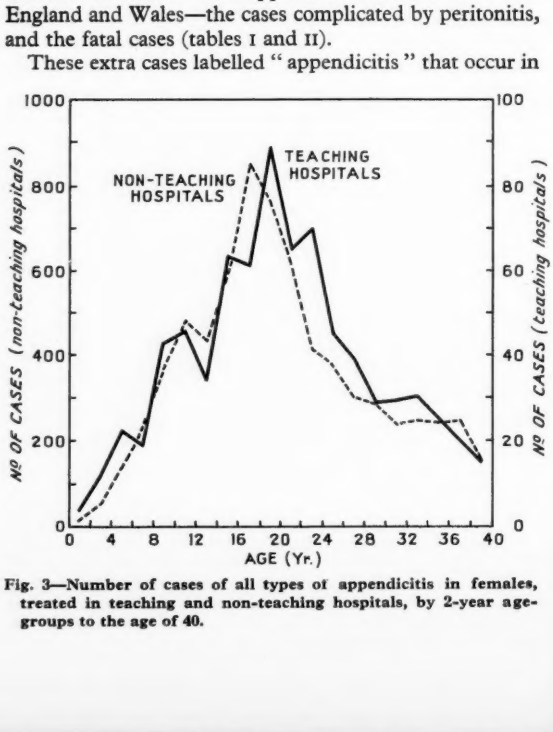

Fig. 3—Number of cases of all types of appendicitis in females, treated in teaching and non-teaching hospitals, by 2-year age-groups to the age of 40.

young women are thus probably not due to inflammation of the vermiform appendix as ordinarily understood. There is no adequate evidence of the value of appendicectomy in them (cf. Querido 1959), and no reason to believe that real inflammation of the appendix is particularly likely to occur in young women (cf. Boyce 1949, Bailey and Love 1959). On the other hand, there are a variety of gynæcological syndromes such as "dysmenorrhœa" (Drillien 1946, Lowe and Ferguson 1951) and disturbances of ovulation (McSweeny and Fallon 1950, Collett et al. 1954) which are especially common in young women. These extra cases of "appendicitis" decline rapidly in the early 20s, at a time when the marriage-rate is high. The data reported in this paper show that the incidence of these cases is lower in married than in single women of the same age (table IV), but they also suggest that the incidence declines in both the married and the single during the 20s. The data, therefore, do not support the suggestion that the disappearance of these cases of "appendicitis" in the mid-20s is due to marriage.

The persistence of these cases emphasises the difficulty of the practical problems which they present. These problems are diverse—for some cases present as emergencies while others run a chronic course. The more academic question of the nature of the disease or diseases from which these patients are suffering, and the practical one of management, are linked. Progress with either would help in the solution of both.

One difficulty is numbers. Although these cases of "appendicitis" in young women are common, and the number treated in the country as a whole is large, on the average each consultant general surgeon will only be responsible for the care of about 10 cases a year. While there must be large variation around this figure, the opportunities for an individual surgeon or hospital to collect a substantial series of cases are clearly small. Perhaps for this reason, there appears to be no definitive description of the clinical features of appendicitis in young women which contrasts the features found in cases that were confirmed histologically with those that were not, and compares both with the findings in males of the same age.

The regional organisation of the N.H.S. seems well adapted to tackle this kind of study. It can be estimated that each year in the Welsh region, which is one of the smaller ones in terms of population but one for which the necessary figures happen to be available (G.R.O. 1959), 500 more cases of "appendicitis" are treated each year in females aged 15–24 than in males of the same age. If all cases diagnosed as "appendicitis" and aged between 15 and 24 in all the hospitals of a region, and the associated teaching hospital, were reported in uniform detail to a regional committee, the clinical findings on sufficient cases could be analysed. It would be important to include the teaching hospital, because these problems appear to be as difficult in these hospitals with their greater resources as they are in the non-teaching. At the same time the histological reporting on the tissues could be done "blind" without reference to the clinical features. Such a study should make it possible to establish, for example, which pre-operation features were associated with unequivocal inflammation of the appendix; and whether there were any associations between clinical features and less definite histological changes. Further, it would also be worth comparing the female cases where the patient had been seen by a gynæcologist before operation with those where she had not.‡ Perhaps in some hospitals all female patients suspected to be suffering from appendicitis could be seen routinely by a surgeon *and* a gynæcologist. The subsequent history of a representative sample of patients operated on for "appendicitis" might also be studied.

Are these problems worth solving? There is no evidence that appendicectomy helps these patients. The blocking of beds and the diversion of surgical facilities is not small. The use of this operation and diagnosis may well be delaying a better understanding of the disorders in question.

SUMMARY

The difficulties of the diagnosis of appendicitis in young women are well known. An attempt has been made to discover the number who undergo appendicectomy but are probably not suffering from inflammation of the appendix.

In National Health Service hospitals of England and Wales this number is 7000–8000 each year; since the start of the service there have probably been about 100,000 such operations. The number of girls of 17 discharged from hospital with the diagnosis of appendicitis is twice what might be expected. On the other hand, young women show no excess of appendicitis complicated by peritonitis, or of fatal appendicitis.

These cases are as common in the teaching as in the non-teaching hospitals, and their number is not declining.

A collaborative study of the clinical and pathological features of all cases described as "appendicitis" in young people, in one or more hospital regions, might throw light on this disease.

The General Register Office of England and Wales kindly made the special tabulations of the data from the National Hospital Inpatient Inquiry which they carry out jointly with the Ministry of Health. I am grateful to Mr. R. A. Brews, F.R.C.O.G., and Prof. I. Doniach, M.D., of the London Hospital, for helpful criticism, and to Prof. W. T. Irvine, F.R.C.S., who was also at the London Hospital when this work was done. I have had many useful discussions of this study with Prof. J. N. Morris and my colleagues of the Social Medicine Research Unit.

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‡ No record was made of the proportion of patients who were seen in consultation with a gynæcologist. There is no reason to believe that many were operated on by gynæcologists.

SCHIZOPHRENIC SYNDROME IN CHILDHOOD

SINCE May of last year, on the invitation of The Hospital for Sick Children, Great Ormond Street, a working party [1] have been considering the characteristics and recognition of those severely disturbed children sometimes referred to as psychotic. The first necessity, they found, was to clarify and agree on terminology. Some members preferred the more general term " psychosis in childhood ". to " childhood schizophrenia "; but eventually it was agreed that " schizophrenic syndrome in childhood " should be used, and the following nine diagnostic " points " were accepted:

1. Gross and sustained impairment of emotional relationships with people. This includes the more usual aloofness and the empty clinging (so-called symbiosis); also abnormal behaviour towards other people as persons, such as using them, or parts of them, impersonally. Difficulty in mixing and playing with other children is often outstanding and long-lasting.

2. Apparent unawareness of his own personal identity to a degree inappropriate to his age. This may be seen in abnormal behaviour towards himself such as posturing or exploration and scrutiny of parts of his body. Repeated self-directed aggression, sometimes resulting in actual damage, may be another aspect of his lack of integration (see also point 5), as also the confusion of personal pronouns (see point 7).

3. Pathological preoccupation with particular objects or certain characteristics of them, without regard to their accepted functions.

4. Sustained resistance to change in the environment and a striving to maintain or restore sameness. In some instances behaviour appears to aim at producing a state of perceptual monotony.

5. Abnormal perceptual experience (in the absence of discernible organic abnormality) is implied by excessive, diminished, or unpredictable response to sensory stimuli—for example, visual and auditory avoidance (see also points 2 and 4), and insensitivity to pain and temperature.

6. Acute, excessive, and seemingly illogical anxiety is a frequent phenomenon. This tends to be precipitated by change, whether in material environment or in routine, as well as by temporary interruption of a symbiotic attachment to persons or things (compare points 3 and 4, and also 1 and 2).

(Apparently commonplace phenomena or objects seem to become invested with terrifying qualities. On the other hand, an appropriate sense of fear in the face of real danger may be lacking.)

7. Speech may have been lost, or never acquired, or may have failed to develop beyond a level appropriate to an earlier stage. There may be confusion of personal pronouns (see point 2), echolalia, or other mannerisms of use and diction. Though words or phrases may be uttered, they may convey no sense of ordinary communication.

8. Distortion in motility patterns—e.g. (*a*) excess as in hyperkinesis, (*b*) immobility as in katatonia, (*c*) bizarre postures, or ritualistic mannerisma, such as rocking and spinning (themselves or objects).

9. A background of serious retardation in which islets of normal, near normal, or exceptional intellectual function or skill may appear.

These points were not intended as absolute criteria in the sense that all, or any particular one, must be present: nor were they designed for use as a rating scale. Though no attempt was made to arrange them in order of importance, it was found, when they were tested by different members of the group, that the first was present in all but 1 of 68 children. Many members of the working party regarded the ninth also as a sine-qua-non.

This interim report, which appears in full in the October issue of the *Cerebral Palsy Bulletin*, concludes by saying: " We do not doubt that further improvements could be made, and it is with this aim in view that we offer our contribution at this stage for comment and criticism—based preferably on trial ". Offers of collaboration (forms would be supplied) or other communications arising from this will be welcomed by the chairman, Dr. Mildred Creak, at The Hospital for Sick Children, Great Ormond Street, London, W.C.1.

1. The members are: Dr. Mildred Creak (chairman), Dr. Kenneth Cameron, Dr. Valerie Cowie, Miss Sylvia Ini, Dr. Ronald Mac Keith, Dr. Guy Michell, Dr. Gerald O'Gorman, Mr. Frank Orford, Dr. W. J. B. Rogers, Dr. A. Shapiro, Dr. F. Stone, Dr. George Stroh, and Dr. Simon Yudkin.

Public Health

CONTROL OF INFECTIOUS HEPATITIS IN A BOARDING SCHOOL BY γ-GLOBULIN

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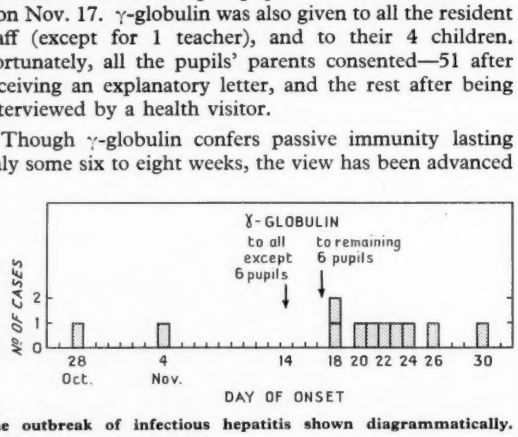
IN the autumn of 1960 there was an outbreak of infectious hepatitis in Loddington Hall Boarding Special School for educationally subnormal pupils. The school is a large stone-built country house near Kettering. On Nov. 7, 1960, the visiting medical officer reported sending a case of infectious hepatitis to the local isolation hospital the previous week, and diagnosing a further case. There were then 57 resident pupils, 32 boys and 25 girls, between the ages of ten and sixteen, and 8 members of the staff with 4 children of their own.

Hæmatogenous infection could be excluded because none of those affected had received any injections in the past six months. To control the infection, γ-globulin was administered to all except 6 pupils on Nov. 14, and to the 6 on Nov. 17. γ-globulin was also given to all the resident staff (except for 1 teacher), and to their 4 children. Fortunately, all the pupils' parents consented—51 after receiving an explanatory letter, and the rest after being interviewed by a health visitor.

Though γ-globulin confers passive immunity lasting only some six to eight weeks, the view has been advanced



The outbreak of infectious hepatitis shown diagrammatically.

that in a closed community subjects thus protected are likely to suffer from subclinical attacks after the temporary immunity has waned. In this way so-called passive/active immunity of a more permanent nature is established. 2·5 ml. γ-globulin was administered to children who were ten or under, or small for their age, and 5 ml. to the others.

There had already been 2 cases before γ-globulin was given. Thereafter 9 further pupils became ill, the last on Nov. 30, within 16 days of first receiving γ-globulin (see figure).

Since the incubation period is long and variable—from ten to forty days, commonly twenty-five—it is reasonable to assume that these 9 children were already incubating the disease when γ-globulin was administered.

There were no further cases in the autumn term or in the subsequent two terms, when the school was under special supervision. 4 pupils left at the end of the autumn term; 3 new pupils were admitted at the beginning of the spring term, and 1 a few weeks after term had begun.

Apart from giving γ-globulin, the measures for promoting hygiene in the school were reviewed, and paper towels were provided. No other steps to control the spread of infection were called for.

A study of the way the beds were arranged in the dormitories, and the seating in the diningroom, indicates that infection was spread by personal contact, presumably by droplet infection. The 11 cases were distributed as follows: two dormitories with 3 each, two with 2, and one dormitory with 1 case. In three instances pupils occupying adjacent beds were affected.

Clinically all the cases were mild, the later cases particularly so—in fact, children were sent to hospital with slight icteric staining of the sclerotics and darkening of the urine. In some of those admitted to hospital, jaundice was not detectable in artificial light. In addition to icterus, the main symptoms were abdominal pain, vomiting, nausea, and anorexia; headache was less frequent. In one or two instances there was a definite prodromal phase, lasting a few days, with pyrexia and malaise. The urine was free of bile in from two to nineteen days after admission to hospital, the stay in which ranged from thirteen to thirty-seven days, with an average of twenty-four days. None of the patients relapsed.

Krugman et al. (1960), in a study of the effect of γ-globulin in an institution for mentally defective children in New York, found that when the dose was increased from 0·01 ml. to 0·06 ml. per pound of body-weight, the incidence of hepatitis decreased tenfold to thirtyfold. With the smaller dose the reduction was two-and-a-half-fold. At Loddington Hall School the amount of γ-globulin administered represented, for the boys, 0·071 ml. to 0·034 ml. per pound of body-weight, with an average of 0·048 ml.; and, for the girls, 0·089 ml. to 0·037 ml., with an average of 0·052 ml. It will be noted that the dose of γ-globulin at Loddington Hall School was approximately 0.05 ml., which is close to the dose of 0·06 ml. given in the New York institution.

Summary

An outbreak of infectious hepatitis in a boarding special school for educationally subnormal pupils was apparently controlled by the administration of γ-globulin.

I should like to thank the headmaster and his wife, Mr. and Mrs. D. J. Prunier, for their cooperation and help in controlling the outbreak, also the visiting medical officer, Dr. J. Lawson Matthew, for his assistance, Dr. R. Wigglesworth, consultant pædiatrician to the Kettering and District General Hospital, for permission to study the hospital case-notes, and Dr. E. T. Roden, of the Ministry of Health, for his advice.

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Conferences

PÆDIATRIC SURGERY

THE British Association of Pædiatric Surgeons held its annual meeting, overseas for the first time, in Stockholm on Sept. 12–14, under the presidency of Mr. D. J. WATERSTON.

Respiratory Distress

PETTER KARLBERG (Stockholm) remarked that in infants large changes in ventilation followed even small changes in the calibre of the air passages. Serial determinations of the pCO_2 and pH of blood were sometimes important in the control of respiratory distress in infants and could be made by micro methods on 0·25 ml. of capillary blood. R. E. BONHAM CARTER (London) distinguished three groups of children with respiratory distress: (1) those who could not get air in, (2) those who could not get it out, and (3) others who had difficulty in both inspiration and expiration and in addition could not properly utilise the little air they could get in. He emphasised the increasing importance of reduced mobility of the diaphragm in small infants.

Congenital vascular rings cause tracheal obstruction at a very early stage in development by interfering with normal growth. D. J. WATERSTON (London) pointed out that division of the ring was not followed by sudden improvement. If the ring was really causing respiratory disturbance before operation the disturbance continued despite operation since it was due to organic narrowing of the trachea. Forcible expansion by the anæsthetist of the very small lung sometimes found in association with a left-sided diaphragmatic hernia was dangerous because rupture of air spaces might lead to leakage of air into the pleural cavity; lobes of this type often expanded spontaneously within 24 hours.

There was general agreement that endotracheal intubation was necessary for infants, but L. OKMIAN (Stockholm) employs ether analgesia, whereas A. STEAD (Liverpool) prefers nitrous oxide and a relaxant. To some extent this choice of agent is limited by the preference of some surgeons for diathermy in order to reduce bleeding in the wound.

E. ABERDEEN (London) gave three reasons for tracheostomy: (1) to bypass an obstruction in the airway, (2) to improve drainage of the lungs, or (3) to reduce the dead space, the last two being the commonest. He suggested that if, instead of cutting out a segment of cartilage, two tracheal rings were incised there was less chance of stenosis of the trachea after removal of the tracheostomy tube. M. FEYCHTING (Stockholm) pointed out that too small a tube may not provide any relief and that the largest tube which will fit snugly in the trachea must be chosen, especially if a mechanical respirator is to be used. He spoke of the need for asepsis in managing a tracheostomy, especially during cleaning and replacement of the tube and aspiration of the bronchial tree. The formation of crusts of secretion in the tube or below it in the trachea is evidently unaffected either by the type or composition of tube used or (in the opinion of most speakers) by the attempts of the nursing staff to prevent crusting. In G. HAGLUND's (Gothenburg) clinic 0·25 ml. 0·9% saline is squirted into the trachea every 15 minutes and is coughed out by the patient. The difficulty of maintaining 100% humidity in the air inside the incubator is now widely recognised, but increasing the humidity of the inspired air does appear to reduce crusting.

A. STEAD pointed to the value of the old-fashioned type of double tracheostomy tube with an oval opening in the upper surface of the outer tube when attempting to reestablish laryngeal respiration.

Mechanical respiration has been extensively used in Sweden. A. SWENSSON (Stockholm) said that the main principle of the method was so to adjust the volume and tension of air in the system that the machine takes over respiration from the

patient, thus saving this part of the total physical effort. It has been used mainly after prolonged apnœa in children with pulmonary infection and collapse—for example, following rupture of the anastomosis after operation on œsophageal atresia. Swenson described also its use to overcome the fixation of the diaphragm and anterior abdominal wall in peritonitis with associated poor respiratory exchange and secondary vascular disturbance. In both his patients there was severe abdominal distension and stagnant peripheral circulatory failure which had not been improved by the intravenous administration of fluid. Notable and almost immediate improvement took place when artificial respiration with an Engstrom respirator and a tracheostomy was started.

Lower-urinary-tract Obstruction

D. I. WILLIAMS (London) discussed the diagnosis and operative treatment of urethral valves and stricture. He pointed out that the narrowest part in the urethra in the child is at the penoscrotal junction, whereas in the adult it is in the bulb, and that strictures in the child appear quite soft and dilate easily but are often very resistant to treatment. In his opinion there is incontrovertible evidence in support of fibroelastosis in one type of posterior urethral obstruction in male children—an opinion which did not meet with general acceptance. N. O. ERICSSON (Stockholm), discussing posterior urethral valves, the commonest form of obstruction in this region in the male child, emphasised that a voiding cystourethrogram was essential. Of those cases in which dilation of the urinary tract was restricted to the posterior urethra, enuresis was present in 67%, whereas infection was found in only 8%. When the dilatation affected the upper urinary tract as well, enuresis was found in only 32% but infection in 66%. Resection of the valves had reduced upper-urinary-tract dilatation in 21 of his 36 cases, and of his entire series only 2 had incontinence after operation and none had strictures. In congenital bladder-neck obstruction endoscopy alone or with cystourethrography was not enough; the neck must be observed during voiding cystourethrography. Infection, which was found in 80% of his cases, was cured by operation in only about half.

U. RUDHE (Stockholm) said that in lower-urinary-tract obstruction due to urethral valves it was essential to find out firstly the site of the valve and the degree of the obstruction which it was producing, and secondly the state of the bladder wall and the degree of dilatation of the urinary tract. He believed that this could be done only by a micturating cysto-urethrogram in addition to intravenous pyelography and retrograde urography. He had found that trabeculation of the bladder was not usually gross, diverticula were uncommon, but reflux was present in two-thirds. The common feature in all was some change in the bladder neck with indentation of the urethra from behind and from both sides. He had not found any radiological evidence that fibroelastosis was a factor in any of his cases, and a deficient detrusor activity was found in only 1. He did not agree that emptying of the bladder depended on the abdominal musculature. P. P. RICKHAM (Liverpool) described the depressing situation found in the advanced stages of lower-urinary-tract obstruction, and pointed out that removal of the obstruction usually did little good. In about 40% of the cases the disturbance was too bad for primary relief by operation and there was a mortality of over 60%. Suprapubic cystostomy had been employed for the very large distended bladder, which in some cases had caused so much enlargement of the abdomen that it had been an indication for caesarean section. In one baby, despite such distention of the bladder that it had burst into the peritoneal cavity, renal damage was not severe and at the age of 5 years the pyelograms appeared normal. On the whole his experience of suprapubic cystostomy had been disappointing, and the results of primary nephrostomy also had been poor.

The problem of urinary diversion has not yet been solved, and a wide search is still being made for a satisfactory solution to this difficult and common problem. It seemed clear from the discussion that cutaneous ureterostomy was probably the best measure to obtain survival in very ill children.

Ulcerative Colitis

TH. EHRENPREIS (Stockholm) reviewed the cases of ulcerative colitis which had been treated in the four children's hospitals in Stockholm and showed that the incidence of this disease had increased considerably. In the 9 years to 1960, 23 patients (27% of the total) were operated on, the indications being perforation of the colon, fulminating disease, total disablement for 1 year, or partial disablement for 5 years. 7 of these operations were undertaken as acute emergencies. The operation which was chosen depended partly on the degree of involvement of the rectum. In 10 colectomy and anastomosis of the ileum and the rectal stump was done when the rectum was not involved. In 8 others moderate involvement of the rectum led to ileostomy with colectomy, and in 5 in whom there was severe rectal involvement the colon and rectum had to be excised. The rapid improvement and gain in weight which was constantly observed after operation was associated with only 2–5 stools a day in those in whom the ileum was joined to the rectum, but with rather more frequent movements when ileostomy remained. A recent psychiatric investigation of the patients treated by operation showed remarkably good tolerance of the ileostomy and no difference between those treated surgically and those who had responded to conservative treatment.

Cryptorchism

O. QVIST and C. G. BERGSTRAND (Stockholm) had reviewed fertility after operation for bilateral cryptorchism. They had reviewed the results of 44 operations in 35 boys 20 years earlier. They found that the operative technique had not influenced the anatomical results; 14 were fertile, 6 were possibly fertile, and in the remainder there was severe impairment of fertility or sterility.

Tracheo-œsophageal Fistula

M. LYNN (Rochester) had reviewed the clinical features of tracheo-œsophageal fistula without atresia in more than 200 published reports and in 5 patients of his own seen in 3 years. In only 41 of these accounts was there a good description of the site of the fistula, 22 being at the thoracic inlet, 10 in the neck, and only 9 in the thorax. The undoubted features of this anomaly were coughing during feeding, abdominal distension on crying, spluttering when drinking water, and recurrent pneumonia. Many of these children had died during radiological examination; and œsophagoscopy or bronchoscopy was not usually of much help, especially as a number of the orifices were obscured by a fold of mucosa. The best way to diagnose the condition at necropsy was by opening the front of the trachea and searching its back wall. Diagnosis was probably best made by listening to the chest while feeding the child or allowing it to drink, the diagnosis being confirmed by radiological examination.

Body-water

J. LISTER (London) described the method of measuring the total body-water in the newborn child with tritiated water. With the permitted dosage of 1·3 μC per kg. body-weight the concentration of tritium in the body-water was so low that samples gave only a few more counts per minute than the background. The total error of the method was ±3·6%, and a larger dosage was clearly essential to produce reliable results.

Megacolon

J. KOSTIA (Helsinki) reviewed the results of treatment of 89 cases of megacolon in 68 of which the cause was Hirschsprung's disease; in 21 of these there was an associated anal atresia. Most of the cases of Hirschsprung's disease had been treated either by Swenson's or Duhamel's operation. There were a good many infective complications after the Swenson operation, most of which were due to leaks at the suture line: an abscess formed in 4, there was a stricture in 6, intestinal

obstruction in 4, and other complications such as peritonitis in 3. 3 of the 28 patients died after the Swenson operation, but only 1 out of 28 after the Duhamel operation—a baby whose colon was already perforated at the time of operation. A colostomy was done in only 3 of the Duhamel series and in 11 of the Swenson series. Only 2 of the patients had intra-abdominal complications after the Duhamel operation, but there was mucosal prolapse in 4; soiling had persisted since operation in 10 of the 28 treated by the Duhamel method but in only 2 of a similar series treated by Swenson's operation. All the patients treated by the Duhamel method, however, were still under the age of 4 years. The Duhamel operation was technically easier and freer from complications even in infancy than either the State or Swenson type of operation, and a colostomy was seldom needed. This view received a good deal of support in the subsequent discussion.

Congenital Cardiac Disorders

In a guest lecture the PRESIDENT described the steady reduction in the age of patients submitted to operation on account of patent ductus arteriosus and coarctation of the aorta. The mortality was related to the severity of the original functional disturbance and was much lower than when these patients had been treated without operation.

Œsophageal Reconstruction

In the second Liverpool lecture G. PETTERSSON (Gothenburg) said that in œsophageal reconstruction he had never pulled the stomach up into the chest in a child. His experience with operations which bypass the stomach was disappointing, and this procedure might interfere with growth. He pointed to the dangers of using the ascending colon because of the vulnerable vascular pedicle which might be pressed against the pylorus when the ascending colon was used; but this technique was rather safer if the colon was taken up behind the stomach. There was no agreement about the optimum time for reconstruction of the œsophagus in œsophageal atresia for which a primary anastomosis could not be done. Delay increased difficulties within the family, and since all these children needed repeated operation the sooner definitive surgical treatment was begun the better. His own preference at present was for a primary reconstruction on the first day of life, using the transverse colon on the middle colic pedicle.

CANCER CHEMOTHERAPHY

A SYMPOSIUM on the use of methotrexate (' Amethopterin ') in the treatment of cancer was held in London on Sept. 18, under the chairmanship of Prof. F. BERGEL.

Methotrexate (4-amino-*N*10-methyl-pteroylglutamic acid) and mercaptopurine (' Aminopterin ', 4-amino-pteroylglutamic acid) are folic-acid antagonists, which, as Prof. E. BOYLAND remarked, interfere with nucleic-acid synthesis by inhibiting folic-acid reductase. The reduction of folic acid to folinic acid (citrovorum factor) is inhibited not only in the malignant-cell nucleus but also non-specifically in other tissues, leading to severe systemic toxicity. This is best overcome by the administration of citrovorum factor.

Mr. W. P. GREENING has used methotrexate in the treatment of advanced breast cancer either alone or in conjunction with ovariectomy. Improvement was observed in 6 of 17 (35%) patients without ovariectomy and in 14 of 20 (70%) patients who also underwent ovariectomy. These figures do not reveal its precise value, but are sufficiently encouraging for methotrexate to be considered in further clinical trials, particularly in patients for whom other remedies have been abandoned.

Dr. K. D. BAGSHAWE assessed its use with mercaptopurine in 9 patients with chorionepithelioma—a tumour which can be anticipated to show some response since actively dividing fœtal and maternal tissues require large amounts of folic acid. In 6 of these 9 patients not only clinical and radiological remission but also hormonal remission was obtained, for chorionic gonadotrophin was no longer found in the urine. 2 patients died of cerebral metastases; and the 9th, although still alive, has become drug-resistant.

Others have had mixed success with methotrexate in the management of chorionepithelioma. Prof. I. DONALD (Glasgow) had 1 strikingly good result, and Dr. EVE WILTSHAW has noted tumour regression in 4 instances; whereas Mr. A. E. R. BUCKLE was unsuccessful with 2 patients: 1 died; and the other appeared to become resistant to the drug, so he was forced to try actinomycin and chlorambucil instead.

Dr. BAGSHAWE has endeavoured to overcome such resistance by combining methotrexate with mercaptopurine. This may account for his gratifying results, although it is difficult to be sure with a tumour which has an unpredictable course, punctuated occasionally by spontaneous remissions.

Dr. E. N. MOYES (Worcester) obtained good initial results with methotrexate in the treatment of 2 patients with trophoblastic tumours involving the lungs, but both eventually died. Dr. A. M. JELLIFFE also drew attention to the particularly bad prognosis of trophoblastic tumours in the male.

Mr. A. C. MUIR (Bradford) suggested that the toxic effects of the drug on the vulval mucosa might influence leukoplakia. On this premise, 3 patients with leukoplakia and 19 with carcinoma of the vulva, ovary, or uterine body or cervix were treated with this drug. He was unable to claim clinical or histological improvement in this series; 1 patient died of acute yellow atrophy, but this could have been a sequel to serum-hepatitis.

Dr. R. D. SULLIVAN (Boston) has adopted Beerman's technique of intra-arterial regional perfusion to provide a high local concentration of drug in the malignant area. Fluorescein is injected through the intra-arterial catheter in situ, and the region to be perfused is displayed by ultraviolet light. This defines where the tip of the intra-arterial catheter is lying and helps to prevent perfusion of the brain instead of, say, the tongue. A continuous intra-arterial infusion of methotrexate is then delivered in dosage of 50 mg. per 24 hours for an adult. It is accompanied by intermittent injections of citrovorum factor, 6 mg. in 6 hours, to neutralise the toxicity of the folic-acid antagonist. By this means, Dr. Sullivan and his colleagues have obtained complete regression in 9 of 51 malignant neoplasms of the head and neck, in which disease was restricted to the area under treatment; partial improvement was obtained in a further 4. Regression was complete in 2 of a series of 6 patients with carcinoma of the cervix. He emphasised that the technique was a team effort, and thus far it remains in the province of research rather than accepted clinical practice.

Mr. G. WESTBURY has used this method at the Westminster Hospital since July, 1960, in cancer of the head and neck (32 patients), limbs (4), cervix (2), and liver (1) and has been particularly gratified with the rapid relief of pain. He has gradually reduced the dose of methotrexate from 50 mg. daily, in order to judge the optimum which can be given without simultaneous citrovorum factor; this seems to be 3 mg. daily for 6 days. If the tumour invades both sides of the midline of the head or neck area, then regional perfusion should first be concentrated on one side followed by similar maximum dosage to the other side.

Mr. H. J. ESPINAR (Bristol) was also favourably impressed by regional perfusion with methotrexate, following his experience in 22 cases of carcinoma predominantly in the head and neck area. He suggested that the drug should be given initially, and that, if this chemotherapy failed, radiotherapy should be applied.

Dr. B. LAURANCE (Derby) recalled the value of the drug in leukæmia in children, for it was in this disease that Dr. Sidney Farber, of Boston, had originally claimed good results with mercaptopurine in 1948, and methotrexate was subsequently found to be effective. Dr. Laurance has given methotrexate intrathecally with good effect when the meninges and skull have been involved.

The proceedings are to be published.

In England Now

A Running Commentary by Peripatetic Correspondents

Through *Folia* I wander, there where'er a green
Arch Path unfolds before me all *Nature* is serene.
Amidst a myriad murmurs that set the air a-hum
My lone *Vox Sang* and sings to sweet *Ann Surg* " I come ".

Oh, she's an *Angiol*, for her throughout that land
Brave men have desperate ventures planned,
Acta Hæm and *Rad* and *Scand*,
Such deeds as are recorded true
Whene'er the *Zodiac* shows anew
Conjunct the fearful *Cancer Bull*
In the dark *Chronicle of WHO*.

" Come fly with me ," I cried, " that jocund priest,
Rev Belge, shall marry us ", but gently she her hand released
And said, " Alas, by the great *JAMA*, no
It cannot be, for my stern *Onkol* ne'er will let me go."

If to have loved and lost as then I did
Was sweet, what boots it ever after to exclaim *Ibid*?

* * *

It is axiomatic in our family that when we set out for the holidays "the car always turns north". Though we always aim for the Highlands, we never go to the same place twice. This year we chose Lochcarron, and had it consistently wet, but we enjoyed it.

Each year we go to whatever Highland Games may be locally accessible. Strome Ferry advertised a " Sports "—a subtle difference that succeeds, we were told, in avoiding entertainment tax by eliminating piping and dancing. The day was wetter than most, but everyone had a high old time. The men, not in the least incommoded by the constant drip from their caps, discussed the price of heifers, and the ladies sat in the tea-tent and discussed everything else. The children muddied themselves with abandon, and the dogs barked.

Our children had a good day, none more than Margaret (aged 14), whose consumption of sweets is abnormally high even for our family. As soon as she realised that there were money prizes, she entered for every race. At the end of the day, straggly-haired but triumphant, she was richer by 9*s*. The subsequent engorgement of carbohydrates lasted all the way back to England. Margaret is a strong supporter of the car's northing instincts.

* * *

He was an almost euphoric East Anglian rustic type, and he was having his left hydrocœle excised next day. After the examination he beckoned me back to his bed. " Tell me, doctor, how much are you really going to do then ?" I reassured him. However, his question proved merely an excuse for launching into a discourse that might have been entitled " Some Fen thoughts on orchidectomy ". I listened spell-bound. He wouldn't mind, he admitted, if his left stone were removed, but his right—ah, now that was different. His mother had told him that, and she knew. Chap had fallen from a tractor once on the farm; hurt his right stone, not his left, mind. Afterwards he were no good—no good at all. I admitted I hadn't heard of this. Ah well, he couldn't help that. It were a fact. Anyway, he weren't worried, not with it being his left side.

I wonder ? Jenner and the milkmaid, Withering and the old lady with the foxgloves. . . . Could there be just the tiniest grain of truth . . . ? Hey, come off it!

* * *

I always take trouble to explain any technical terms to my patients. So I sympathise with the lady who lately rang up a Defence Ministry about her son. " His skin trouble came on at puberty," she said. " You know—when they take the ' O ' level."

Letters to the Editor

CHRISTMAS GIFTS FUND

SIR,—I should be grateful if you would allow me space to make the customary annual appeal to enable the Royal Medical Benevolent Fund to send a Christmas gift to each of the Fund's regular beneficiaries. The Fund does remarkably good work by providing grants and annuities to those members of our profession and their near relatives whom misfortune has rendered unable to provide for themselves, but this does not allow for any extra expenditure at Christmas. That is why this special appeal is made.

The medical profession is generous-minded and I am sure that it will only need this reminder to ensure a liberal response sufficient to gladden the hearts of our beneficiaries this Christmas.

Would donors kindly send their contributions, marked " Christmas Gifts " to the Royal Medical Benevolent Fund, 37, St. George's Road, Wimbledon, London, S.W.19.

ZACHARY COPE
President,
Royal Medical Benevolent Fund.

LIMITATIONS OF MEDICAL CARE ATTRIBUTABLE TO MEDICAL EDUCATION

SIR,—Professor McKeown (July 1) attributes our present deficiencies in medical education largely to " traditional restrictions of the responsibilities of teaching hospitals " and quotes in support the glib remark of the Webbs that the voluntary hospitals took what was interesting while the public hospitals were left with what was difficult.

No doubt there was a grain of truth in the Webbs' remarks, but it might be more accurate to say that voluntary hospitals took patients they could help and sent elsewhere those they could not. Since then I suspect the picture has changed. For instance, in the teaching hospitals in Sydney today the average age of patients in the medical wards is over 60. There is no shortage of patients with chronic irreversible disease of the brain, the heart, the lungs, the liver, and the kidneys. The outpatients provide a fair quota of chronic locomotor disorders. If one cares to look for them, disorders of the mind are equally prevalent. The problem of the teacher in this country is to find young patients with acute disease suitable for clinical clerking. This, we think, is necessary since acute illness still forms the greater part of the young doctor's work in practice.

Turning to research, I gather that Professor McKeown attributes our lack of understanding of mental and chronic illness to segregation of patients with " incurable " disease in non-teaching hospitals. Does anyone imagine that we would have overcome G.P.I. by bringing all cases under the surveillance of university teachers ? Would we hasten progress in disseminated sclerosis, schizophrenia, mental deficiency, and, say, atheroma in this way ? Knowing what we do about mongolism and 21-trisomy, would any purpose have been served by doing the same for mongols ?

What evidence is there that the " solution of a large range of medical problems requires study of representative patients drawn from known populations " ? True, we may gain some insight into the " ætiology of congenital malformations, toxæmia of pregnancy, and the nature of essential hypertension " by epidemiological methods, but

I suspect that experimental medicine in its widest sense may continue to have the last word.

In his book *Medical Education*, Flexner wrote that " systems, though never alone decisive, are as such important, inasmuch as the ideals they embody and the conditions they set up tend either to promote, depress or dissipate effort ". Mindful of the rich harvest of the last thirty years, would it not be wiser to allow progress in chronic diseases to proceed naturally as our conceptual thinking and technology advances, rather than dissipate the time and efforts of university teachers on problems most of them are in no position to solve ?

In a changing world it is prudent to keep medical care and medical education under constant review. I suspect that many would differ from Professor McKeown in the diagnosis and the treatment of our present disabilities.

School of Medicine,
University of New South Wales,
Kensington,
New South Wales.

R. B. BLACKET.

RESEARCH ON TEACHING METHODS

SIR,—Professor Erskine and Dr. O'Morchoe (Sept. 23) have done a real service to medical education. My own experience, as an undergraduate and in teaching both on the Continent and in this country, confirms their conclusions. May we hope that theirs is only one of a series of investigations designed to put educational method in medicine on a rational basis. And may I suggest that the selection of teachers deserves high priority.

That gifts for research, clinical work, and teaching are rarely combined in one person is well known. Few composers are also good instrumentalists, conductors, and academic musicians. And vice versa. In medicine we shall have to acknowledge that the ability to teach ought to be tested, before candidates for an academic career, well qualified in research and clinical acumen, are admitted to posts mainly devised to train doctors.

One way would be an annual selection course for registrars and senior registrars, lasting a few days only, in term time, and held at a different university each year. A committee of equal numbers of junior and senior students, lecturers, and professors (say, 12 in all) would (1) listen to a lecture of 30 minutes on a subject chosen by the candidate; and (2) discuss with him for another 30 minutes a subject chosen for him by a professor in his own specialty.

The many qualities required of a good teacher would get a a fair chance of being demonstrated in front of those who are being taught and those who teach.

A certificate of fitness to teach ought to be given or withheld according to the pooled assessment within the committee. Those who succeed would obtain valuable support in applying for a teaching post. The others would be wise to concentrate on their proved ability in other spheres.

In a letter there is no room for further detail. But there can be little doubt that some such scheme is overdue.

Aylesbury, Bucks. L. S. MICHAELIS.

MORTALITY AND MORBIDITY IN THE ATMOSPHERE

SIR,—It is an interesting commentary on the current approach to " clean air " that your annotation of Sept. 23 makes no mention of internal air pollution by smoking. Similarly, the forthcoming annual conference of the National Society for Clean Air will not be discussing this aspect of the problem. And yet, here we have a " man-made " form of air pollution which is " amenable to solution by direct experiment ". Some detailed analyses are urgently required of the air in confined public places where smoking is still permitted—and what could be a more suitable, and more pertinent, venue than the average " chest " ward ? Subjectively, the prevailing air conditions therein are usually worse than anything encountered outdoors except during a smog.

There is now much evidence that smoking is one of the " variables " which must be considered before drawing conclusions about the effects of general air conditions. As Bignall [1] observes: " It seems likely that the effect of air pollution in causing the less severe forms of complicated bronchitis may have been exaggerated and that cigarette smoking is a more important factor." But Phillips et al.[2] anticipated this: " . . . in studies of chronic respiratory complaints of all types, unless the factor of cigarette smoking is considered and comparisons are drawn between smokers and non-smokers, the conclusions drawn may not be valid." It was their opinion that " . . . inhalation of tobacco smoke seems an extreme form of air pollution, exceeding other forms by a wide margin."

Do let us remember that clean air, like charity, begins at home—in more senses than one.

Newton Heath,
Manchester. J. P. ANDERSON.

LUBRICATION OF JOINTS

SIR,—I know that I am expressing the mind of my coauthors in describing your recent annotation (Sept. 23) as a very fair presentation of the views of the high contending parties about joint lubrication. Our book, which you have done us the honour of referring to, does not, of course, deal solely with this topic; but in it we have undoubtedly given much attention here and there to this problem, which we believe to be basic for the interpretation of the structure of synovial joints. Since the book was published Mr. Charnley has reiterated his believe that in so far as synovial fluid is a lubricant it acts merely as a boundary lubricant.[3] The opposition between this view and our own is complete, for boundary lubrication precludes that flow of the synovial fluid (for however short a time) that is the essential mark of film lubrication. Mr. Charnley's opinion was understandably strengthened by the experimental work carried out on his behalf by Tanner and Edwards.[4] But this opinion was strongly challenged by other engineers at the time, notably by Clayton[5]; and in their reply to this expert on lubrication these two engineers conceded that they had difficulty in reproducing the actual working conditions of the joints in an engineering laboratory.

Again since our book appeared, a paper of fundamental importance for the whole of lubrication theory has been published by Archard and Kirk.[6] These workers have investigated the lubrication of bearings having point-contact when at rest under conditions of size, loading, and speed which include the whole physiological range encountered in the diarthroses. Their work followed upon the study of line-contact systems by Crook.[7] These two papers complete in essentials that generalised theory of fluid lubrication which Dr. R. O. Boswell told me in 1932 would have to be done in time and on which (he felt) a study of biological lubricated systems could throw much light because of their very generality of structure as contrasted with the surfaces of revolution necessarily employed by the engineers at that time. The investigations of Archard and Kirk were carried out with the most recent and exact techniques. Their conclusion, supporting that of Crook, was that hydrodynamic lubrication occurs much more frequently

1. Bignall, J. R. *in The Medical Annual*; p. 424, Bristol. 1961.
2. Phillips, A. M., Phillips, R. W., Thompson, J. L. *Ann. intern. Med.* 1956, **45**, 216.
3. Charnley, J. *Lancet*, 1961, i, 1129.
4. Tanner, R. I., Edwards, F. J. Institute of Mechanical Engineers, Symposium on Biomechanies, 1959, p. 21.
5. Clayton, D. *ibid.* p. 47.
6. Archard, J. F., Kirk, M. T. *Proc. roy. Soc. A*, 1961, **261**, 532.
7. Crook, A. W. *Phil. Trans. A*, 1958, **250**, 387.

and boundary lubrication much less frequently than is usually supposed. They say explicitly that the experiments they conducted covered a range of conditions, particularly with heavy loads or with very low speeds, where hitherto it had been assumed that only boundary lubrication could occur. Amongst other things, they showed that mutual deformation of the bearing surfaces (such as actually occurs in our joints) is no bar to the formation of that kind of lubricant film which we have postulated, and that it is indeed a help towards it when the load is increased. Furthermore, these workers have shown that an effective lubricant film must have a certain thinness rather than thickness. The probable importance of the synovial pads in this connection had been pointed out earlier [8 9]; the inference has been strengthened lately by the recent paper of Davies and White,[10] who have shown how these pads are maintained in being even in severe fat starvation.

The work of McCutchen [11] with his consequent hypothesis of " weeping " lubrication has to do with the engendering of the lubricant film immediately upon the start of movement and with the maintenance of that adhesion of the fluid to the fixed and moving surfaces which is essential for fluid-film lubrication. The essence of the fluid-film type is that the fluid does flow between the surfaces during movement. This in turn demands an internal streamlining of the joint cavity with, upon occasion, the provision of such special structures as the intra-articular disks and menisci, so formed and arranged that they help rather than hinder this streamlining. Apart from its consonance with the most modern studies of lubricated systems, the hypothesis of fluid-film lubrication is one which articulates an otherwise disjointed mass of anatomical facts. It not only " saves the phenomena ", as Newton would have said, but it also has led to a considerable body of further studies explicitly designed to test its truth and its theoretical consequences. But this is a tale too long for telling here.

Department of Anatomy,
University College,
Cork. M. A. MACCONAILL.

ANDROGENS IN ANÆMIA

SIR,—I hope a cursory reading of your excellent leading article of Sept. 9 will not encourage the unwary to use androgens in the treatment of aplastic anæmia in children without a balancing dose of corticosteroids.

The dose of methyltestosterone advised by Shakidi and Diamond [12] is large—2 mg. per kg. body-weight daily—perhaps ten times greater than a virilising dose for children. The effect of androgens in childhood is to produce acne, hirsutism, " breaking " of the voice, phallic hyperplasia, and advancement of height and skeletal maturation. These side-effects of therapy might be regarded as unimportant compared with the successful treatment of an implacable disease. One of these complications however—advanced skeletal maturation—cannot be reversed and must inevitably produce eventual stunting of the child's growth.

It is of great physiological interest that these effects are largely controlled by the opposing action of corticosteroids, whether the balancing action is mediated through their anti-anabolic action on protein metabolism, by a direct effect on anterior pituitary hormones (growth hormone and thyrotrophin) or by both mechanisms. In any case, methyltestosterone should not be used in the treatment of aplastic anæmia in children without the addition of prednisolone or another corticosteroid. In one patient reported by Shakidi and Diamond in whom the corticosteroid was inadvertently omitted, the skeletal maturation (bone-age) advanced by four years. The dose of corticosteroid used should be small (say, 0·2–0·4 mg. prednisolone per kg. body-weight daily) and the correct dose is that which allows an average height gain and does not advance skeletal maturation. Height should be regularly plotted on a chart and a radiographical assessment of skeletal maturation should be made every three months.

The Children's Hospital,
Birmingham. DOUGLAS HUBBLE.

" IATROGENIC "

SIR,—I am sorry to see the word " iatrogenic " in your editorial last week. Surely nothing can be iatrogenic except a doctor's mother?

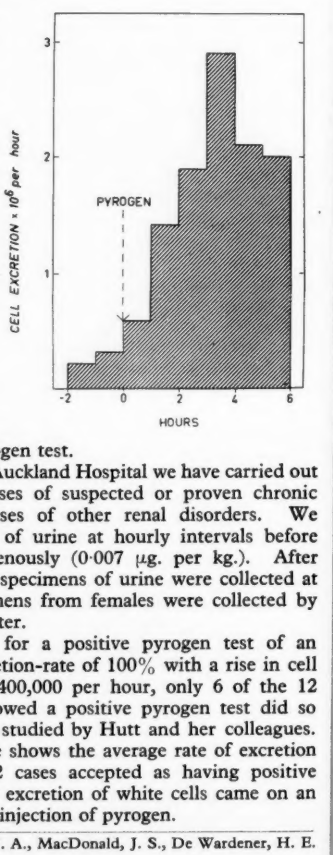
Hoccombe,
Somerset. J. A. BOYCOTT.

THE PYROGEN TEST

SIR,—We are concerned that many cases of chronic pyelonephritis, with an increased excretion of white cells in the urine after giving pyrogen, may be missed if the test is carried out as described by Hutt et al.[1]

Pears and Houghton [2] showed that after injecting pyrogen (' Pyrexal ', Wanders) there was an increased excretion of white cells in the urine of most patients with chronic pyelonephritis. Three specimens of urine were collected at intervals of 30 minutes before injecting pyrogen intravenously (0·007 μg. per kg. body-weight). Four specimens of urine were then collected at half-hourly intervals starting from the time of injection. The excretion-rate of white and non-squamous epithelial cells in 17 patients with chronic pyelonephritis showed a marked increase within 30 minutes, followed by a gradual fall in the cellular excretion over the next two hours.

Hutt et al. obtained results similar to those of Pears and Houghton. The test was modified so that before the pyrogen was given urine was collected over a 4-hour period. After injecting pyrogen two further specimens of urine were collected at hourly intervals. The higher of the two white-cell excretions after the injection was compared with the initial value. The urinary excretion of white cells after giving pyrogen rose by more than 100% to more than 400,000 cells per hour in 11 of 14 patients with untreated chronic pyelonephritis. A response of this type was " arbitrarily defined " as a positive pyrogen test.



In the medical unit at Auckland Hospital we have carried out a pyrogen test in 16 cases of suspected or proven chronic pyelonephritis and 8 cases of other renal disorders. We collected two specimens of urine at hourly intervals before injecting pyrogen intravenously (0·007 μg. per kg.). After the injection, six further specimens of urine were collected at hourly intervals. Specimens from females were collected by indwelling urethral catheter.

Using Hutt's criteria for a positive pyrogen test of an increased white-cell excretion-rate of 100% with a rise in cell excretion to more than 400,000 per hour, only 6 of the 12 cases who eventually showed a positive pyrogen test did so within the 2-hour period studied by Hutt and her colleagues. The accompanying figure shows the average rate of excretion of white cells in the 12 cases accepted as having positive pyrogen tests. The peak excretion of white cells came on an average 4 hours after the injection of pyrogen.

8. MacConaill, M. A. *J. Anat.* 1932, **66**, 210.
9. MacConaill, M. A. *J. Bone Jt. Surg.* 1950, **32B**, 244.
10. Davies, D. V., White, J. E. W. *J. Anat.* 1961, **95**, 30.
11. McCutchen, C. W. *Nature, Lond.* 1959, **184**, 1284.
12. Shakidi, N. T., Diamond, L. K. *New Engl. J. Med.* 1961, **264**, 953.

1. Hutt, M. S. R., Chalmers, J. A., MacDonald, J. S., De Wardener, H. E. *Lancet*, 1961, i, 351.
2. Pears, M. A., Houghton, B. J. *ibid.* 1959, ii, 1167.

These findings are at variance with the observations of Pears and Houghton.[2] Earlier work on pyrogens, however, has shown that bacterial endotoxins produce a fever only after a latent period of 30–90 minutes.[3]

Auckland Hospital, Auckland, New Zealand.
J. Z. MONTGOMERIE
J. D. K. NORTH.

RECRUITMENT AND TRAINING OF MENTAL NURSES

SIR,—Dr. O'Gorman's Point of View (Sept. 23) makes interesting reading, but I still feel that the main problem is one of pay.

One hears comments that if we increased the pay, then the wrong people would be attracted to the profession, but in answer I would say that we should raise it so high that we could be selective in our choice of nurses. I also feel that there might be some grounds for a system of gratuities at five-year intervals in order to retain the services of our nurses.

The other aspect that I think should be studied more closely is that all the modern appliances should be available to make the nurses' task less "odious"—i.e., mechanical sluices, the use of disposable materials, and a more suitable nurse's uniform and protective clothing. In fact, we should do all in our power to make an unpleasant job as pleasant as possible, since this job has to be done.

South Ockendon Hospital, Romford, Essex.
GORDON DUTTON.

STAPHYLOCOCCAL PULMONARY INFECTION

SIR,—May I raise one aspect of the penultimate sentence in the valuable contribution made by Mr. Mitchell and his colleagues (Sept. 23) to the understanding of pulmonary infections with staphylococci in hospital. To imply that the incidence of such infections may be diminished by operating, especially in the elderly, as soon as possible after admission to hospital may seem to sanction the common practice of inadequate preparation of the respiratory tract for anæsthesia and surgery.

All surgical units willingly delay operation because of anæmia or heart-failure, but few even stop to inquire whether the respiratory tract is fit for the intended procedures (in a contaminated environment) unless the patient is so obviously incapacitated that a fatality would appear inevitable.

It could be argued that the hospital staphylococcus would have small pathogenic powers if the respiratory tract which it colonises was a healthy one. Pre-existing lung disease is not confined to Lanarkshire, yet it is still uncommon for patients undergoing elective operations to have more than a cursory clinical examination or to have a preoperative X-ray of the chest.

No surgeon would be careless enough to operate without evidence that the urine had been tested for obvious abnormalities; a preoperative chest X-ray surely stands in exactly the same relationship.

No anæsthetist will embark on anæsthesia without knowing the patient's blood-pressure, but many have in the past been prepared to narcotise and paralyse patients for serious operations without making any inquiry into even the simplest ventilatory performance.

The preparation of the respiratory tract for operation also demands a clean mouth, and oral sepsis is about as prevalent as chronic bronchitis.

Until we can find time to take trouble adequately to prepare the respiratory tract for operation, so long shall we be cursed with postoperative complications including staphylococcal invasion and its dire consequences.

We have pressing waiting-lists and too few physiotherapists as an excuse, but this should not blind us to the natural history of the problem.

The situation can be controlled by the anæsthetists, by their understanding of respiratory physiology and their right to refuse to anæsthetise the improperly prepared patient.

Thoracic Surgical Unit, Churchill Hospital. Oxford.
C. GRIMSHAW.

TREATMENT OF DISC LESIONS

SIR,—I find it very hard to accept your statement (Sept. 16, p. 642) that tears and protrusions of the annulus—by which I presume you mean tears of the annulus and protrusions of the nucleus—usually require surgical removal.

In a series of over 200 cases of low back pain treated under the care of Mr. Leslie Morris in the orthopædic department of the Leicester Royal Infirmary there were 143 cases of sciatica; the rest complained only of localised backache. When one considers that the diagnosis is divided between 64 cases of intervertebral disc protrusion, 53 of osteoarthritis, 48 of lumbosacral strain, 25 of sacroiliac strain, with 25 sundries, it can be seen that sciatica covers a very much wider range than intervertebral disc lesions. When you say that about 20% of those with incapacitating sciatica or lumbago have atypical clinical signs, we have to match this with the fact that of our 223 cases in only 6 was no definite diagnosis reached, the others in the 25 "sundries" being 6 with a "pre-disc", 2 with fibrositis, 2 with shingles, 2 with kyphosis, 2 spondylitis, 1 fracture, 1 high disc, 1 central disc, 1 with tuberculosis, and 1 with neurosis. But the single point with which we would take issue is this statement of the need for surgical removal of tears of the annulus and protrusions of the nucleus. In over 8 years' experience of the treatment of low backache in the outpatient department, involving at a rough estimate 4000 cases (which, according to the present 6 months' survey, would include 1000 cases of intervertebral disc lesion), only about 10 or 12 have been considered for operation, and of these only 6 were actually operated on. Of the 6 operated on 4 are no better than when they were first seen. In contrast to this, in our present series, of the 64 cases of intervertebral disc lesion, 53 were placed in plaster. In 7 of these relief was immediate, in 10 within one week, in 19 within two weeks, in 5 within three weeks, and in the remaining 12 within one month. No patients were unrelieved.

In our opinion the treatment of backache resolves itself first of all into an accurate diagnosis and then into short-wave diathermy and exercises for osteoarthritis, radiant heat and exercises for lumbosacral and sacroiliac strain, and the application of a plaster cast for intervertebral disc lesions. This 6 months' survey was undertaken because of two lectures delivered to the Leicester Medical Society by Sir Harry Platt, then president of the Royal College of Surgeons, and Dr. James Cyriax, of St. Thomas's Hospital. These two lectures, the first one deprecating active treatment in the form of plaster casts and operation, and advising rest in bed, and the second advocating manipulation without anæsthesia, threw an unfavourable light on the efficacy of our own treatment. In our opinion plaster casts in the treatment of intervertebral disc lesions have been completely vindicated.

That the tests mentioned in your leader can help to determine whether operation should be advised, I have no doubt. Indeed, anything which would postpone operation in a case of intervertebral disc lesion should be encouraged, because in our experience conservative treatment, if pursued long enough, will result in good spinal function in the vast majority of cases. As you so wisely say, experience in this country points to the truth of this outlook, and we are more apt to advise the patient to tolerate a certain amount of pain, at any rate for a time. Unfortunately, you seem to imply that only disc degenerations

3. Grant, R., Whalen, W. J. *Amer. J. Physiol.* 1953, **173**, 47.

cure themselves spontaneously, and annulus tears and nucleus protrusions need operation.

Apart from the evidence of our investigation, I have the personal experience of a cricket accident before I started medicine at the age of 32, which in retrospect I recognise as a disc protrusion and which was cured by 10 days in bed without the intervention of a doctor. As a medical student I played football until qualified and afterwards up to the age of 45 and am still playing cricket, so are you saying that I ought to have been operated on at 32? And I am only one example of thousands who, so far from getting to the orthopædic outpatient department, never even go to their own doctor, and their annulus tears and disc protrusions heal just the same.

Is there any wonder therefore that in America—where the cost of treatment is high, where doctors feel the need to "sell medicine to the American public", and where conservative treatment would often end in the patient going elsewhere—is there any wonder that operation is still advocated in the face of the success of conservative methods?

The one common factor in those cases which fail to reach the doctor at all and those which we treat either by physiotherapy or plaster casts is, in my opinion, the relief of muscle spasm. One pointer to the truth of this is the success of cold-spray treatment with 'Skefron' as advocated by Ellis at the Leeds General Infirmary.

Great Glen, Leicestershire. G. A. STANTON.

OVERDOSE OF CHLORDIAZEPOXIDE

SIR,—I was interested in the report of changes in the electroencephalogram (E.E.G.) described by Dr. Thompson and Dr. Glen (Sept. 23) as I have recently carried out a preliminary investigation into the effect of chlorodiazepoxide on the E.E.G., and found changes similar to those described by Kaim and Rosenstein.[1]

Fast activity, as found by Dr. Thompson and Dr. Glen, was the commonest change, associated with normal doses of chlorodiazepoxide (15–45 mg. daily), and occurred in 24 of 41 cases.

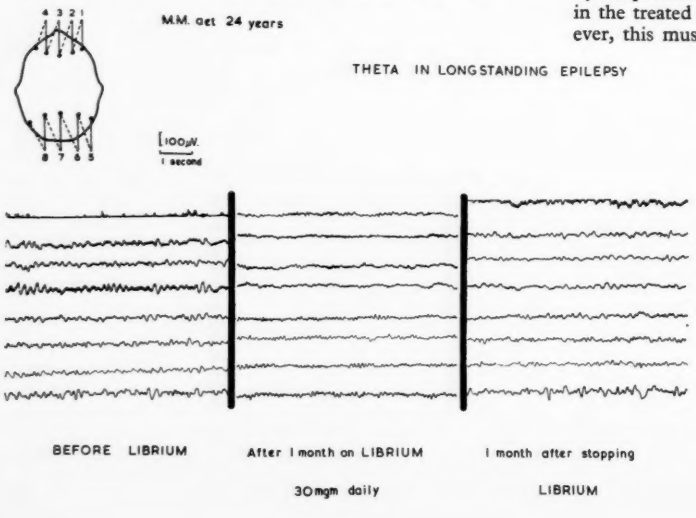
There are other more dramatic and unusual changes, however, which can broadly be described as a tendency for the E.E.G. to become normal (see accompanying figure). Thus, in the 41 cases, 17 showed a reduction of paroxysmal discharges, 23 showed a reduction or disappearance of abnormal background slow activity (theta), and 18 showed an increase in normal alpha activity.

Unfortunately, while there may be clinical improvement in association with E.E.G. improvement, this is not always so, and equally one may get clinical improvement without much E.E.G. change.

The effect of chlorodiazepoxide on the E.E.G. and its action as an anticonvulsant in major and minor epilepsy and in infantile spasms is most interesting and deserves further study.

All Saints Hospital, Birmingham. P. M. JEAVONS.

1. Kaim, S. C., Rosenstein, I. N. *Dis. nerv. Syst.* 1960, **21**, (suppl.) 46.



ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

SIR,—In his letter of Aug. 19 Dr. Poller objected to our study reported in your issue of Aug. 12 on the grounds that our series did not fulfil his requirements for objective assessment. Dr. Poller implied that the comparability between our treated and control group is highly questionable.

If Dr. Poller carefully rereads our paper he will find that the two groups in our series will satisfy any statistical analysis for comparability in terms of size, age of patients, sex-distribution, associated diseases, recurrent infarction, period from onset and supportive therapy—all the requirements Dr. Poller mentions. We feel confident therefore that we have achieved a satisfactory random distribution of cases into treated and untreated groups.

Dr. Poller suggests that our results would have been different if we had adopted a more "modern" therapeutic approach. First, he raises the question of the effectiveness of subcutaneous heparin therapy. It has been shown, however, that subcutaneous heparin (25,000 units twice daily) produces a sustained prolongation of the coagulation time (as opposed to the intermittent intravenous administration of heparin).[1] Secondly, he implies that dicoumarol is an unsuitable drug to use. We are not aware of any convincing evidence of the superiority of the newer anticoagulants compared with dicoumarol. In a study like ours where the patients are covered by heparin until dicoumarol takes effect, the difference in the rapidity of the action of the different drugs is of no importance.

Dr. Poller states that we have given our patients less than the optimum amount of dicoumarol, but since he is informed about the excellent results obtained elsewhere in Scandinavia with a regimen comparable to ours, he suggests that our test-systems are inadequate and that "faulty reagents or technique may be the cause of the poor results in the Danish hospitals".

In reply to the latter criticism, we would emphasise that Owren's P. & P. test was closely standardised in the group of laboratories in the investigation, and that the tests were adequately controlled at regular intervals.

That the treatment we gave was effective is demonstrated by the pronounced reduction in thromboembolic complications in the treated group. As the mortality was unchanged, however, this must mean that the prognosis in acute myocardial infarction is determined by factors not influenced by anticoagulant therapy.

We are disappointed that, according to Dr. Poller, a short-term controlled trial of anticoagulant treatment in acute myocardial infarction—even if morally justifiable—would be physically impossible in Britain. We hope this attitude does not extend to other forms of treatment in common use today. Moreover, we do not feel that "the fact that the medical journals have been assuring us of the value of anticoagulants since the early 1940s" can be taken as a proof of the efficacy of such a treatment.

We are pleased that the remarks of Dr. Deutsch (Sept. 9) give us an opportunity to amplify our original report of Aug. 12. Mr. Deutsch asks whether the patients were able to

1. Refn, I., Raaschou, F., Vestergaard, L. 1st International Conference on Thrombosis and Embolism, Basel, 1954; p. 758. Basel, 1955.

choose which hospital they would attend. This was not so. All admissions to the municipal hospitals in Copenhagen are arranged through a central office. Neither this office nor the general practitioners had any information of the trial going on. The possibility of the patients choosing a treating or not-treating department was completely excluded.

As to the question whether any specific cause of death might have been accumulated in the treated or the not-treated group we can answer that we have evaluated the causes of death in every patient. Thrombo-embolism, cardiac rupture, and hæmorrhage as a cause of death were mentioned in our paper. Several other causes of death were registered: congestive heart-failure, cardiac arrhythmias, shock, new coronary thrombosis, sudden death from unknown cause, and complicating diseases. The distribution of the different causes of death was equal in the treated and the not-treated group and no specific accumulation was observed.

Medical Departments 2 and 3, Kommunehospitalet,
Medical Departments B and C, Bispebjerg Hospital,
Copenhagen, Denmark.

TAGE HILDEN
KURT IVERSEN.
FLEMMING RAASCHOU
MICHAEL SCHWARTZ.

THE DUMPING SYNDROME

SIR,—May I suggest that Mr. Cox and Mr. Allan (Sept. 23) reexamine their basic assumptions before drawing conclusions about the effects of fat ingestion after partial gastrectomy?

In one case at least the dumping syndrome can be induced by the ingestion of raw milk or strong sugar solutions almost without fail, whereas the same patient regularly eats bacon and two eggs with fried bread for breakfast without a qualm. That a man dumps after a mixture of egg, milk, and sugar does not prove that fat is at fault. This seems to be an extreme case of the sin of confounding in research.

Plymouth. F. T. WHEELDON.

MUMPS 1961 AND SEVERE NEPHRITIS

SIR,—Your interesting annotation [1] raised the question of the unusual prevalence of some of the less common complications, specifically "gastroenteritis" perhaps ascribable to mumps pancreatitis. You alluded to the probable value of long-term studies of the natural history of such acute infections as mumps, mentioning the possible rewards of statistical study of increased liability to pancreatitis or diabetes in later life. Some evidence of this type was presented, relating, in 4-year successive periods, mumps epidemics to diabetic deaths in Norway among juvenile diabetics in the pre-insulin era.[2] Careful prospective studies of the relationship of acute infections to various parenchymatous diseases of later years might be most illuminating.

As to less common complications of mumps in 1961, we have this year observed two children and been advised of a third who, within 10–14 days of the onset of parotitic mumps, developed severe nephritis (in each case fatal), all lacking serological and cultural evidence of concomitant β-hæmolytic streptococcal infection. The details will be published later.

There is now abundant experimental and clinical evidence that viruses frequently rest utterly unsuspected within the cells of numerous organs of man and other species. (The kidneys of normal monkeys used in tissue-culture work have yielded an annoying array of unexpected unwanted simian viruses.)

The role of latent viruses in the ætiology of diverse parenchymatous degenerative disorders of later life is an enigma difficult to explore, but which may prove to be important when appropriate laboratory techniques for study are evolved. The application of the epidemiological method via sound multiphasic prospective studies may be even more revealing. In today's age of specificity when one seeks *the* cause and *the* cure, revival of the concept of precipitating *and* contributory causes for various conditions may be refreshing.

1. *Lancet*, 1961, i, 1389.
2. Gundersen, E. *J. infect. Dis.* 1927, **41**, 197.

Department of Pediatrics, University of Louisville School of Medicine, Louisville, Kentucky.

ALEX J. STEIGMAN
WALTER T. HUGHES
HENRY DELONG.

PREGNANCY AND MALIGNANT MELANOMA

SIR,—Your leading article of Sept. 9 concludes that a woman with this disease "can still bear children with a reasonable assurance that thereby she will not have compromised her chance of ultimate survival". The studies on which this conclusion is based compared the survival-rates among women becoming pregnant after diagnosis with the survival-rates among non-pregnant women of the same age. This method of analysis clearly introduces bias into the results.

The mortality in the pregnant group before the onset of pregnancy must necessarily be nought. If the time of diagnosis is used as a basis, as was done in these studies, survival-rates would therefore be higher in the pregnant group than in the control group if pregnancy had no effect on the course of the disease. If on the other hand, the survival-rates were calculated from the time of onset of the pregnancy and compared with the survival-rates from the same point in time in matched controls, this systematic error would be eliminated. Unfortunately the material from these studies on pregnancy and malignant melanoma is not given in sufficient detail to permit such an analysis.

As pointed out in one of the studies, another source of bias would arise if the woman least ill were more likely to become pregnant. This seems likely and selection of this kind could be avoided only in a strict clinical trial, which for obvious reasons cannot be undertaken.

The two types of bias entering into these studies would result in a better prognosis among pregnant women if pregnancy had no effect on the course of the disease. The fact that no significant difference was found in the survival-rates of the two groups might, therefore, indicate a harmful effect of pregnancy. At least it does not seem warranted without further analysis to assure a woman with malignant melanoma that pregnancy will not reduce her chances of recovery.

Cancer Registry of Norway, Oslo. KNUT MAGNUS.

TESTING OF PHARMACEUTICAL PRODUCTS IN GENERAL PRACTICE

SIR,—Some time at the end of last year a small but enthusiastic group of general practitioners was organised with the object of assessing and appraising new products or new angles on existing products. This experiment was successful and the numbers increased, being consolidated as the "G.P. Field Research Unit". This unit is now functioning busily and has established a friendly liaison with many of the pharmaceutical houses. Policy as regards receiving fees for the work has been the subject of much internal discussion, and we finally feel that we would offer a more ethical approach if we remained an unpaid service, accepting only the actual expenses of the trial.

Until the end of the trial the name of the firm participating is known only to the organiser; so neither bias nor favouritism, however unconscious, can be shown. A true assessment is the object.

This group would welcome inquiries from enthusiastic

practitioners—particularly those who have specialised knowledge of some branch of medicine—who would care to join us. As stated, our policy is to offer a free service to the pharmaceutical houses and to cover all the actual expenses of the trial.

In making this scheme more widely known, we should be glad to hear the views of others from both sides.

The G.P. Field Research Unit,
130, Well Hall Road,
Eltham, London, S.E.9.

W. H. MYERS
R. S. COLTMAN.

ICE ARREST OF THE HEART

SIR,—Mr. Ross (Aug. 5) described two methods of preparing a mush of saline-ice crystals for ice arrest of the heart. We have found a modification of his second method to be more convenient and far less time-consuming.

Instead of glass bottles, plastic bags containing 500 ml. saline each are frozen in a freezing mixture (about −5°C). The bags are now and then (2–3 times an hour) lifted out of the freezing solution and squeezed and massaged in the hands for half a minute or so. In this way *all* the saline may be changed to a mush of ice-crystals, without any solid parts as often happens when glass-bottles are used, even when the bottles are often and vigorously shaken. By Ross's methods, the contents of the bottles are separated into two parts—ice crystals with less than 0·9% sodium chloride and supernatant fluid with more than 0·9% sodium chloride, which at least from a theoretical viewpoint is undesirable.

Department of Cardiology, and
The Pharmacy,
Copenhagen County Hospital.

MOGENS JØRGENSEN
A. POROTNIKOFF.

HORMONE CONTROL OF BREAST CANCER

SIR,—The workers associated with the preliminary communication by Dr. Hale (Aug. 12) are to be congratulated on what must surely have the possibilities of a real advance. At first sight the introduction of a cannula into a breast tumour may appear abhorrent, but the immediate, real advantage must be weighed carefully in the advanced and hopeless cases in which there is little to lose.

The vaginal smear " sort out " method which we have devised does not give an immediate indicator, but points to the possibilities without a tumour puncture. A high cornification (pyknotic) œstrogen count would need suppression. Conversely, for a very low count over a 28-day cycle, stilbœstrol may be required. When these counts are graphically recorded against the tumour response, the results may be very pretty (figs. 1 and 2).

We have, for many years, been using ^{32}P with external

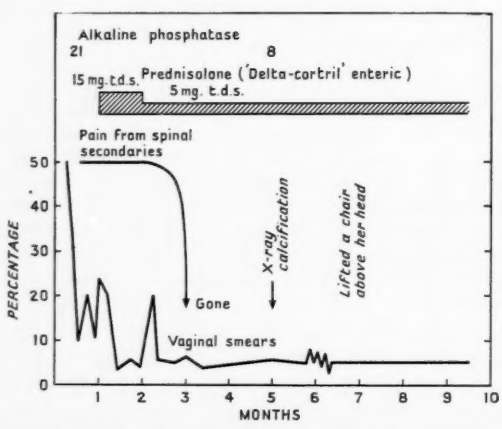


Fig. 1—Suppression for secondaries in bone in a woman of 62.

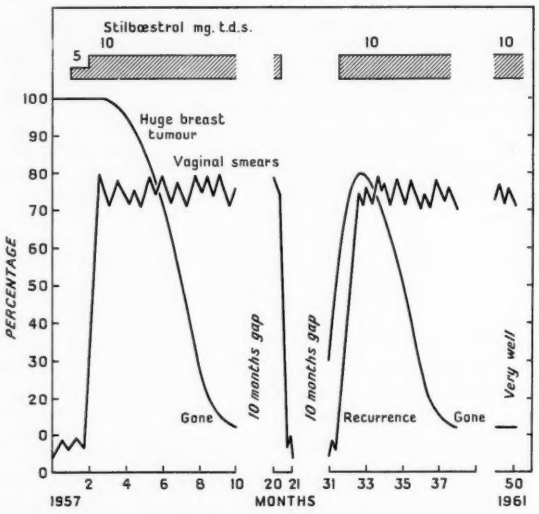


Fig. 2—Good response to œstrogens in a low-smear case with huge bilateral breast carcinomas, recurrent after radiotherapy. No change from normal stilbœstrol dosage, but neoplasms disappeared after higher dosage, which raised smear count. After stopping stilbœstrol smears dropped and there was a recurrence about ten months later, but a second good response was achieved and the patient is now clinically free of disease.

counting [1 2] as an index of tumour activity, but, like others, we are very uncertain as to how much of this counting is due to the tissue vascular element. Recently we have been using radioactive potassium with more encouraging results, but the short half-life and limitations of availability are trying.

Should the Bristol method prove adaptable to the studies of animal tumours, considerable increase in our present knowledge may accrue, especially if they are observed over a whole cycle and under treatment. There is little doubt that many of us interested in cancer control by hormone and cytotoxic drugs will look forward to a full report at a later date and confirmation from others. We intend to try this method.

Royal Northern and Prince of Wales's
General Hospitals,
London.

ANTHONY GREEN.

ALIMENTARY LIPAEMIA AND ISCHAEMIC HEART-DISEASE

SIR,—Dr. Schön (Aug. 26) is right when, discussing the paper by Dr. Bouchier and Dr. Bronte-Stewart,[3] he emphasises the limitation of estimating plasma-lipid clearance by the intravenous infusion of synthetically stabilised emulsions. We have likewise found that the rate of removal of 'Lipomul IV' from the circulation is similar in patients with ischæmic heart-disease and in normal subjects.[4]

Dr. Schön did not mention, however, that a major objection to the use of synthetic fat emulsions, and probably also to the fat emulsion which he has used himself, is that the fat particles are removed by the reticulo-endothelial system. This is significantly different from the metabolism of chylomicrons which are removed largely by the parenchymal cells of the liver and by adipose tissue probably after hydrolysis by lipoprotein lipase.

For these reasons the use of human chylomicrons is prefer-

1. Green, A. *Proc. R. Soc. Med.* 1959, **52**, 482.
2. Green, A., Godfrey, B., et al. British Empire Cancer Campaign Annual Report, 1960; p. 707.
3. Bouchier, I. A. D., Bronte-Stewart, B. *Lancet*, 1961, i, 363.
4. Mashford, M. L., Nestel, P. J. *Circulation Res.*, 1961, **9**, 7.

able. We have infused human lymph chylomicrons labelled in vivo with ^{14}C-palmitic acid into patients with ischæmic heart-disease and into normal control subjects. The mean rates of removal of chylomicron radioactivity from the chylomicron fraction of the plasmas of these subjects were found to be the same in the two groups. This may have, however, been due to the fact that the mean total esterified fatty acids of the plasmas were similar in the 2 groups. When lymph chylomicrons were infused into 2 subjects with gross hyperlipidæmia the rate of removal of chylomicron radioactivity was considerably less than normal and appeared to be related to the levels of endogenous esterified fatty acids.

Department of Medicine,
University of Melbourne,
Australia.

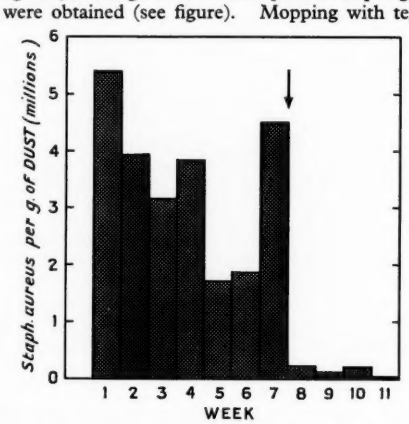
P. J. NESTEL
M. A. DENBOROUGH.

TEGO COMPOUNDS IN HOSPITAL PRACTICE

SIR,—In my preliminary communication [1] I stated that ward floors were being treated with a 1% solution of 'Tego' MHG and the efficacy of the compound was being tested by swabbing the floor with swabs moistened with broth. These swabs were being broken off into salt cooked-meat enrichment medium for *Staphylococcus aureus* and subcultured on to blood-agar after twenty-four hours' incubation at 37°C.

Though after the introduction of tego the number of swabs positive for *Staph. aureus* was reduced, it was thought that a more accurate picture would be obtained by performing counts on the dust by the method of Miles and Misra.[2]

A surgical ward with a floor of thermoplastic tiles was investigated; and high counts of *Staph. aureus* per gramme of dust were obtained (see figure). Mopping with tego MHG



The effect of mopping the floor of a ward weekly with cold 1% 'Tego' MHG. The arrow indicates the start of treatment.

was then introduced and the count thereupon fell to very low levels, sometimes being less than 100 per gramme. Similar results have been obtained from three other surgical wards and a medical ward with floors of mixed terrazzo, composition, thermoplastic tile, welded plastic, linoleum, and wood block.

These experiments have been carried out for eighteen months. Weekly dust samples were taken just before mopping was done. The counts have remained low except when new and over-zealous ward maids have mixed soap with the tego MHG, and neutralised its bactericidal effect.

Damp mopping with tego MHG thus seems to be a useful method for reducing dust-counts of *Staph. aureus*. A fuller report will be published elsewhere together with details of the effect on the rate of wound infection and staphylococcal carriage.

Public Health Laboratory,
Radcliffe Infirmary,
Oxford.

B. R. FRISBY.

1. Frisby, B.R. *Lancet*, 1959, ii, 57.
2. Miles, A. A., Misra, S. S. *J. Hyg., Camb.* 1938, **38**, 732.

TELEPHONE KIOSKS

SIR,—Dr. Odens (Sept. 23) criticises the condition of public telephone kiosks. In towns these are swept and disinfected three times a week and are cleaned even more thoroughly every month. If they are close to main traffic streams they are swept and disinfected daily.

Although we make these efforts to keep our telephone kiosks clean we have, of course, to rely upon the cooperation of the public. It is quite possible for a kiosk to be made dirty within minutes of cleaning.

Dr. Odens refers to "the danger of contamination of infectious diseases from the ear and mouthpieces". In the *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service* of March, 1954, the summary of a paper on the risk of infection from telephones read as follows:

"The mouthpieces and earpieces of a total of 153 telephones, in offices and public kiosks, were examined bacteriologically. No pathogenic bacteria, except *Staph. aureus* and, in one instance a pneumococcus, were found. *Staph. aureus* was present on 7 per cent. of mouthpieces and 18 per cent. of earpieces—an observation that concurs with its known frequency in the nose and throat and on the skin of normal persons. Non-pathogenic mouth streptococci were found in 33 per cent. of mouthpieces.

"Laboratory experiments showed that both *Staph. aureus* and *Str. pyogenes* are able to survive on telephones for several days; but it is only with some difficulty that material artificially inoculated on to telephone mouthpieces can be dislodged by a jet of air similar to that emitted in talking.

"It seems improbable that there is any appreciable risk of respiratory infection being transmitted by way of telephones in ordinary use."

General Post Office,
London, E.C.1.

T. A. O'BRIEN,
Public Relations Officer.

GLOBULINS AND BLOOD-CLOTTING

SIR,—The interesting discussions in your columns have prompted me to present a concept affecting the clotting of the blood in abnormal circumstances, which has not been previously suggested. I have noticed that many whose disease state is accompanied by increases in cryoglobulins and euglobulins may have hæmorrhagic or thrombotic tendencies. In a survey of clinical conditions characterised by increases in globulins, a hæmorrhagic diathesis is seen in 63% to 94% of cases. Thrombosis, in addition to hæmorrhages, was reported in between 3% and 21%. Such cases include multiple myeloma, macroglobulinæmia, and cryoglobulinæmia.

These abnormal proteins when removed by simple means contain large quantities of various clotting factors; almost all the clotting factors present may be found in them, including fibrinogen, prothrombin, factor VIII, and possibly factor V and contact factors. More important is that the complex of these proteins and clotting factors represents a threat, for thrombosis may ensue if these proteins are precipitable and precipitated. This set of circumstances occurs in cryoglobulinæmia where the exposed-skin temperature drops sufficiently to precipitate cryoglobulins in the small blood-vessels of the skin; and the clotting factors which are taken down with them cause thrombosis.

On the basis of these observations, Domz and Feigin [1] treated a patient with essential cryoglobulinæmia with anticoagulants; symptoms were completely relieved and the involved fingers healed rapidly. C. J. Watson and his associates [2] reported successfully treating with anticoagulants the ulcers which occur in this disease.

A central concept of my hypothesis is that the unusual globulins produced in many diseases acquire a capacity for forming complexes with clotting-factor proteins. These clot-

1. Domz, C. A., Feigin, E. V. *Arch. intern. Med.* 1957, **100**, 471.
2. Foley, J. F., Karlen, M., Watson, C. J. *J. Amer. med. Ass.* 1961, **176**, 149.

ting factors are held in a non-functional combination, so the level of clotting factors in the blood-stream in these conditions is commonly decreased. The level of many clotting factors is reduced because many are involved. These combinations may cause thrombosis when they are precipitated.[3–5]

This concept I have named hyperglobulinæmic thrombohæmorrhagic diathesis. My laboratory is working to elucidate the other ways in which " clotting-factor-bearing " abnormal proteins may precipitate.

Los Angeles, California, U.S.A. HENRY H. HENSTELL.

SIX CHILDREN WITH COUGHS

SIR,—I am grateful to Dr. Yudkin (Sept. 9) for bringing attention once again to the need for a wider basis in the training of the doctor. His pertinent question " why has the patient come now? " brings to mind the three questions posed by Dr. Halliday [6]: (1) what kind of person is the patient?; (2) why did he become ill when he did?; (3) why did he become ill in the manner he did? In my own practice these questions have been of great help in reaching the final diagnosis in very many patients.

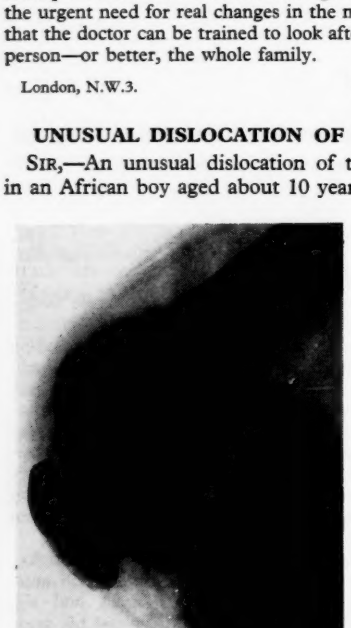
Dr. Yudkin's paper refers only to the mother who presents her child as a " presenting symptom " but, in fact, many adults present a variety of symptoms which " mask " the underlying anxiety or depression that is the real cause of their visit to the doctor. I have described this in more detail elsewhere in a chapter in *Modern Trends in Psychosomatic Medicine*.

The Ministry of Health's new handbook on the Part of the Family Doctor in the Mental Health Service implies that it is the family doctor who should help the psychiatrist treat the patient; but this is an inversion of the truth, since it is the family doctor who should be in charge of his patients (at least when they are at home) and it is the function of the psychiatrist to help the doctor in his task of looking after the patient. Hence the urgent need for real changes in the medical curriculum, so that the doctor can be trained to look after and treat the whole person—or better, the whole family.

London, N.W.3. PHILIP HOPKINS.

UNUSUAL DISLOCATION OF THE PATELLA

SIR,—An unusual dislocation of the patella occurred in an African boy aged about 10 years.



The boy said that three weeks previously he fell down when running. He was able to walk afterwards, then the knee swelled up and became bent. There had been no previous injury. The knee was quite painless but was held fully flexed. A lateral radiograph is reproduced here (unfortunately the anteroposterior film was unsatisfactory).

Under general anæsthesia the displaced patella was manœuvred with the fingers fairly easily forwards and then upwards into its normal position. Because of contraction of the hamstrings the knee could not be completely extended, and the quadriceps extensor tendon was considerably stretched. A back splint was applied.

After 10 days he could lift his leg up off the splint, and after a further 10 days full extension of the knee-joint had been regained. He was discharged able to walk well.

The mechanism of the dislocation (if such it was) is difficult to explain from the history obtained. If this is correct he may have sustained a second minor injury to his knee, which he had forgotten, when the patella was displaced. Alternatively he may have had an uncommonly severe flexion contraction following traumatic synovitis.

Lilongwe African Hospital, Lilongwe, Nyasaland. S. V. HUMPHRIES.

ADVERTISEMENTS FOR HEALTH

SIR,—Dr. Mullins' Point of View, so ably set out in your issue of Sept. 16, has many implications, some obvious, others perhaps less so. One of the less obvious implications is the very great difficulty of writing (whether it be advertisements or a Point of View) without bias and without misleading suggestions.

Was the late George Bernard Shaw perhaps right after all? Rebel though he may have been, he upheld the view that justice was best secured—as in this country—by a system in which the advocate for one point of view put his case (truthfully, naturally) as strongly as possible. The advocate for the contending point of view did the same. Neither was held guilty of *suppressio veri* or of any failure in morality because he omitted to state the opposing point of view. On this rock, Shaw said, British justice was founded and, oddly enough, he upheld it as the best in the world.

No reasonable man or woman would dispute or question for one moment Dr. Mullins' wish for complete objectivity in her approach to this important matter. Nevertheless—as I propose to prove—she approaches the subject with bias.

On p. 649 she says: " Some patients are astonished to hear that buying good food is better than buying expensive vitamin supplements . . . The public is told that it needs a fresh supply of vitamin C every day; but it is not told that this can come from an orange. Much of this kind of advertising may be said to do no harm except to the pockets of those who succumb to it."

We have here a categorical implication (I suggest) that vitamin C tablets every day are more expensive than " an orange " —that their purchase, however, harms only " the pocket of those who succumb " and that those pockets would benefit if they knew about oranges.

The manufacturers of the vitamin C tablets are also, by implication, guilty of *suppressio veri*.

It is, I suggest, Dr. Mullins who is responsible for a misleading implication and therefore of *suggestio falsi* if not *suppressio veri*. It is a simple matter of calculation that if the entire population of this country relied on an orange a day for its vitamin C the total annual cost would approximate to three times the total annual sum paid to manufacturers, not merely for vitamin C, not merely for all vitamin supplements, but for all drugs of whatsoever nature used by the National Health Service.

On Dr. Mullins' own argument, should those who advocate an orange a day for vitamin C not reveal to the public the truly stupendous cost of this source of vitamin C? The fact that those who advocate the use of oranges in this way have no commercial interest in the matter is, I submit, completely irrelevant to the issue of truth or falsity.

I quote this example merely to illustrate the extreme difficulty of directing attention to the merits of one article if it is considered to be axiomatic that one is guilty of *suppressio veri*

3. Henstell, H. H., Feinstein, M. *Amer. J. Med.* 1957, **22**, 381.
4. Henstell, H. H., Kligerman, M. *Ann. intern. Med.* 1958, **49**, 371.
5. Henstell, H. H., Kligerman, M. *Nature, Lond.* 1959, **183**, 978.
6. *Brit. J. med. Psychol.* 1943, **19**, 367.

if one fails to direct attention to all conceivable alternatives and their financial consequences.

An orange a day is a very pleasant supplement to, or indeed part of, the diet for those who can afford it—about £30 per annum at current prices for a family of mother, father, and three children. It is a most extravagant method, however, of supplying vitamin C and would prove to be even more extravagant if national and world demand were stepped up to the extent that it would be stepped up if Dr. Mullins' implied advice were universally acted on.

The same vitamin C which would cost a family of 5 about £30 per annum at today's prices (and more if demand became universal) can be supplied by vitamin-C tablets provided by pharmaceutical manufacturers at a retail cost of about 45*s*. (using 50 mg. tablets). The cost to a hospital on contract would be even less. The average cost to the N.H.S. of all drugs supplied for the same family of 5 is around £10.

I submit that the sentences quoted from Dr. Mullins' article —and others—betray a very heavy bias indeed against manufacturers in their capacity of advertisers.

If Dr. Mullins cannot, from the side-lines, advocate a sincerely held point of view without falling into this pitfall, is it not possible that it is better to avoid asking manufacturers, in the heat of the fray, to aim at standards found impracticable (impossible even) for British justice —and for Dr. Mullins?

H. C. H. GRAVES.
Chairman and Managing Director, Vitamins Limited.

London, W.6.

SIR,—Mr. Graves, who kindly showed me his letter to you, must buy his oranges from expensive shops. As a housewife with a large family to feed I can assure him that I can nearly always buy oranges at 6–7 for a shilling. Half an orange each per day for a family of five comes to about the price of two cigarettes—or £13 a year. But this is not the point. Oranges are not needed in our daily diet any more than are vitamin tablets.

Sir Stanley Davidson and his illustrious colleagues [1] say "all vegetables contain valuable amounts of ascorbic acid, but quantities are variable, and loss in preparation and cooking may be great. However, a single helping of vegetable (3 ounces: 90 g.) daily, even if it has been badly treated by the cook, will usually provide at least 10 mg. of ascorbic acid, an amount known to prevent scurvy."

Lastly, how does Mr. Graves estimate his 45*s*. as the cost of giving a family of five 50 mg. of ascorbic acid per day for a year? To provide it in the form of such tablets as are listed in the *Prescriber's List of Proprietary Medical Products* would cost £3 5*s*. to £4 a year or to give it as Mr. Graves' 'Vitavel' (which also contain other vitamins) would cost 2*s*. 6*d*. a week. And, moreover, prominently displayed in many chemist shops is a vitamin-C preparation which "effervesces" and costs 6*s*. 9*d*. for ten tablets: the cost to the family per year would be £61. How is the housewife to know that she can get the same value for 45*s*., even if she can?

A common defence put up when modern advertising methods are criticised is to complain of "blanket attacks", even when, as in recent articles in *The Lancet*, the criticisms are specific and documented. Is this merely a form of "blanket defence" or does it conceal guilty consciences?

In his letter of Sept. 30, however, Professor Yudkin makes a specific criticism of my recent article. He maintains that a "high-fat" diet is a practical means of persuading patients to consume fewer calories. I agree with him there. But the point in my article which he seems to have missed is that if manufacturers then make "starch-reduced" food which is high in calories, it will no longer be sufficient to tell patients to cut down on starch. Some of my fat patients have recently been gaining weight on a form of "starch-reduced" crispbread which contains more calories per oz. than any other crispbread known to me. It is low in carbohydrate—but it *tastes* like carbohydrate and is as fattening as carbohydrate!

ANN MULLINS.

London, S.E.21.

P.S. My secretary has just typed this and said it showed her why her own slimming efforts stopped being successful a few weeks ago. She stopped eating "starch-reduced" rolls in favour of "starch-reduced" crispbread because it "tastes nicer and more substantial".

1. Human Nutrition and Dietetics; p. 310. London, 1959.

Obituary

WILLIAM BENTLEY PURCHASE

Kt, C.B.E., M.C., M.A., M.B. Cantab., D.P.H., Barrister-at-Law

Sir Bentley Purchase died on Sept. 27 in an Ipswich hospital after a fall from the roof of his house, where he was adjusting a television aerial. For nearly thirty years he was coroner for North London, and he was lecturer in forensic medicine at three London medical schools.

He was born in 1890, the son of the late Sir William Purchase. He was educated at Bradfield and Sidney Sussex College, Cambridge. In 1911 he began his clinical training at the London Hospital, and he qualified in 1914. He departed almost at once with his gunner regiment to France and returned after the war with a brevet majority in the R.A.M.C. and a military cross. He was called to the bar as a member of the Inner Temple in 1919, and took the D.P.H. in 1920 and his M.B. Cantab. the following year. He practised as a barrister from 1921 to 1930, and for most of this time he was Treasury counsel in appeal cases at the London county sessions.

In 1930 he was appointed coroner for North London. For many years he served as secretary of the Coroners' Society of England and Wales, and as lecturer in forensic medicine at the medical schools of the Royal Free Hospital, St. Thomas's Hospital, and University College Hospital. He was also medical officer for the Inner and Middle Temple. From 1948 to 1950 he was chairman of the St. Helier hospital management committee. He was impressed to serve in a number of public and secret activities by Government departments, and he held office as coroner to H.M. Household from 1955 to 1959. In that year he resigned both these appointments, only to be appointed coroner of the borough of Ipswich, where he sat on the day of his death. He was appointed C.B.E. in 1949 and knighted in 1958.

F. E. C. and R. I. M. write:

"Bentley Purchase never grew old. His indifference to any personal discomfort and his magnificent physique enabled him to carry out a programme of life suitable for any three men and yet leave himself time to enjoy the company of his friends in apparent leisure. As a coroner he was superbly qualified by his experience at the bar and in medicine, and by his own fearless integrity, and he will long be remembered as one resolute to maintain the dignity of the office and to adapt it to a changing world. It was as a coroner that the public knew him, but this aspect only showed one surface of a many-faceted character. The other facets which brought lustre to his life make a formidable list: a counsel of erudition and shrewdness; a doctor, practical, humane, and able to impart his knowledge; yachtsman and skier; carpenter and engineer; builder and farmer—one could never fathom the skills and knowledge which he quietly and unobtrusively produced in succession.

"Some will remember his lectures to students, whether of law or medicine, often accompanied by startling or even gruesome demonstrations. Some will remember him in court, for

his sympathy with the bereaved and his impish teasing, alas often incomprehensible to them, of bombastic witnesses. The young will remember him for his generosity to them and their sporting clubs, though he took care to conceal it so far as he could. We remember him as he would wish, we think, to be remembered, in the home of which he was so fond and proud (and so much of which was the product of his own handiwork) —generous, hospitable, kind, indefatigable in our interest, and entirely selfless."

Sir Bentley married in 1924 Beryl Edith Rickards Chapman, by whom he had a son and a daughter.

ANTONI TOMASZ ALEKSANDER JURASZ

M. D. Heidelberg, Hon. F.R.C.S.

Professor Jurasz was the originator of an unusual exercise in international medical education, and many will remember his work as originator and dean of the Polish School of Medicine which was set up within the University of Edinburgh during the late war.

His mother was English, but he was born in Heidelberg where his father held a chair and he qualified there. Much of his career was spent in Poland and in the 'thirties he was professor of surgery in the University of Poznan.

Soon after the beginning of the late war he came to Scotland with other Polish refugees, including a number of medical officers from the Polish Army. Some of these had held senior teaching appointments, many more were young men at different stages of their medical training. At first there was little in this country for these men to do and Jurasz decided to start a medical school. At first he thought of no more than some postgraduate training for those already qualified, but the idea was welcomed enthusiastically, and thanks to the hospitality of the University of Edinburgh and the enterprise of their guests a Polish medical faculty was inaugurated in March, 1941, in the presence of the President of the Polish Republic. In the first year 77 students were enrolled and in due course degrees were awarded with the authority of the Polish Government. Jurasz later made a lecture tour in the United States to collect funds for the Paderewski Hospital for Polish civilians which was started at the Western General Hospital in Edinburgh. He was elected an honorary F.R.C.S. in 1942.

To Jurasz, as he himself once said, the school was symbolic of the need to maintain Western culture in Poland at a time when all the material assets of Polish learning, research, and culture had been destroyed. He had hoped that the Edinburgh school would ultimately move to Poland as part of a post-war renaissance. To his disappointment, owing to the political situation, this did not prove possible, and soon after the Edinburgh school was closed in 1945 he moved to New York where he settled in practice.

Dr. R. Y. STONES

P.M.B. writes:

"I knew Robert Stones closely throughout my whole professional life—indeed since 1905 when we were medical students together at the London Hospital—and come what might, in peace and war, we have kept contact ever since. In his youth he was a good sportsman and I have vivid recollections of him boxing for his hospital against Guy's. He was a plucky hard-fighting opponent with a cracking left which he kept in reserve. He did not force his opinions on others, though he certainly lived up to them. Throughout his career, his motive was to do good to as many as he could, irrespective of race or creed, and he showed this in his latter days when he gave his whole life to the service of Africans."

Diary of the Week

OCT. 8 TO 14

Monday, 9th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. I. H. Mills: Control of Sodium Balance.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, S.E.5
4.30 P.M. Dr. William Evans: To Tell Trash from Treasure. (Wiltshire lecture.)

Tuesday, 10th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Psychiatry.* Prof. E. W. Anderson: Strindberg's Illness (?). (Presidential address.)

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Arthur Jarrett: Keratinisation.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Dr. N. R. Butler: Murder at the Membranes, a National Study of Fœtal Death.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. G. A. D. Gordon: Ulstrasonic Rays in Neurology and Neurosurgery.

Wednesday, 11th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. B. E. C. Nordin: Calcium and Phosphorus Metabolism.

ROYAL SOCIETY OF MEDICINE
5 P.M. *Physical Medicine.* Dr. John Dingle, Dr. J. L. Potter Ætiological Factors in the Collagen Diseases.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: Histology—Epidermal Hyperplasias and Verrucous Nævi.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. W. D. W. Brooks: Spontaneous Pneumothorax.

Thursday, 12th

ROYAL SOCIETY OF MEDICINE
5 P.M. *Ophthalmology.* Mr. John Foster: Oscillosection in Ophthalmic Surgery. (Presidential address.)

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. G. B. Dowling: Classification of Eczema.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Sir George McRobert: From Empire to Commonwealth. (Presidential address.)

ALFRED ADLER MEDICAL SOCIETY
8 P.M. (11, Chandos Street, W.1.) Dr. Walter Schindler: Significance of Puberty in Adult Neurosis.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8 P.M. (Kensington Palace Hotel, De Vere Gardens, W.8.) Dr. A. Doyne Bell: A Brief for the Hospital Architect. (Presidential address.)

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P.M. Mr. Walpole Lewin: Vascular Lesions in Head Injuries.

Friday, 13th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. R. B. Zachary: Neonatal Intestinal Obstruction.
4 P.M. Sir Russell Brock: Present Position of the Surgical Treatment of Cyanotic Heart Disease.

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine.* Dr. Thomas R. Dawber (Framingham, Mass.): The Framingham Enquiry. Dr. M. J. Karvonen (Helsinki): Clinical Surveys in Finland. Dr. Jack Strong (New Orleans): Inter-American Studies of Pathology.

LONDON HOSPITAL MEDICAL COLLEGE, Ashfield Street, E.1
4.15 P.M. Dr. Evans: Cardiology at the London Hospital. (Schorstein lecture.)

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street, Edinburgh, 8
4.30 P.M. Sir Julian Huxley: Evolution of the Higher Primates. (Sir John Struthers lecture.)

Saturday, 14th

FACULTY OF RADIOLOGISTS
9.30 A.M. (University of Edinburgh.) Mr. Andrew Logan: Investigation and Treatment of Carcinoma of the Œsophagus. (Opening of one-day meeting.)

Appointments

Manchester Regional Hospital Board:

HARRIS, I. A., M.B. Adelaide, F.R.C.S., F.R.A.C.S.: senior casualty officer, Lancaster and Kendal hospital group.

JOHNSON, JOHN, M.B. Manc., M.R.C.P.E., D.P.M.: consultant psychiatrist, Oldham and district hospital group.

KEEN, R. I., M.B. Sheff., F.F.A. R.C.S., D.A.: consultant anæsthetist, North Manchester hospital group.

ROGERS, VINCENT, M.B. Lpool, D.M.R.D.: consultant radiologist, Burnley and district hospital group.

Western Regional Hospital Board, Scotland:

FRASER, N. G., M.B. Aberd., D.P.M.: consultant psychiatrist, Woodilee Hospital, Lenzie.

LEISHMAN, W. J., M.B. Glasg., D.A., D.OBST.: assistant anæsthetist, Stirling Royal Infirmary and associated hospitals.

MCEWEN, C. G., M.B. Glasg., D.O.: consultant ophthalmologist, Royal Victoria Eye Infirmary, Paisley, with duties at Greenock, Bute, and Dunoon.

SHANKS, R. A., M.D. Glasg., F.R.F.P.S., M.R.C.P.: consultant pædiatrician, Royal Hospital for Sick Children, Glasgow.

Notes and News

THE ROYAL ARMY DENTAL CORPS

FORTIETH birthdays are not always welcome, but the Royal Army Dental Corps seems to have reached its prime with the celebration of this important anniversary last week. That was certainly the impression given at the clinical meeting and demonstration arranged at the Royal Army Medical College, Millbank, to mark the occasion. Dentistry has advanced in many ways since 1921, and several aspects of its progress were well displayed in a carefully mounted exhibition. The Corps' history was effectively portrayed—from the Order setting it up, signed by Winston Churchill as War Minister, to a demonstration of the latest field dental equipment by the Parachute Field Ambulance.

The R.A.D.C. is threatened with manpower shortages even more severe than those of the R.A.M.C., which are receiving urgent notice.[1] The Corps has a powerful aid to recruiting in the dental cadetships which offer free university training to young men who take a regular commission. The Army can offer to dentists as well as to doctors some splendid opportunities for research. The Army Dental Service has established in the College at Millbank a department of oral pathology, and the striking new survey of the dental health of recruits, described in an annotation on p. 811, is the first important research to come from this department, which will plainly enhance the prestige of the Royal Army Dental Corps.

THE CASUALTY DEPARTMENT

THE latest of a series of planning notes issued by the Department of Health for Scotland deals with the provision and design of casualty and accident departments [2] and gives some interim conclusions reached by the Department's hospital development unit and work-study group.

Pending reports from committees of the Health Services Councils which are reviewing casualty and accident services, certain assumptions had to be made. One was that these services will be concentrated, so far as possible, at general hospitals, each serving a population of at least 250,000. A second was that the casualty and accident department should not undertake the treatment of patients who do not need hospital facilities. And a third was that the department should be in charge of a consultant general or orthopædic surgeon, and with 24-hour consultant cover.

From detailed studies designed to assess the requirements for handling a given load of casualty work, it was evident that present services are sometimes deficient, in staff, in facilities, or in accommodation, or might lack established policy and procedures for the proper treatment of casualties. The note recommends that accommodation should not be subdivided more than necessary; but there should be separate examination/treatment rooms for individual patients, serious injuries should be separated from reception onwards, and clean wounds should be separated from septic conditions at most stages of treatment. In addition, there should be special rooms for certain specific purposes—e.g., waiting, resuscitation. Estimates are given of the staff needed for departments having 50, 100, and 150 new patients daily, and the accommodation is deduced therefrom.

STUDENT NURSES' PLANS

DURING 1960–61 Mrs. Jillian MacGuire made a survey [3] of the first six months of some 300 student nurses in five training schools in the Oxford area, drawing her information from the teachers and the taught. Her criticisms of the arrangements made for the students' introduction to the wards, especially where the school is separate from the hospital, will perhaps be of most interest to those responsible for the nursing curriculum. But the information which she has collected from the students themselves about their reasons for taking up nursing and their plans for their careers should claim a larger and less selective audience.

Of the five schools one was attached to a teaching hospital, and not unexpectedly the students there had taken more subjects in the G.C.E., left school later, and more of them came from professional families. But in the whole group of 292, nearly three-quarters had taken one or more subject at the O level of the G.C.E., and nearly all came from the Registrar General's upper three social classes. How typical these findings would be for nursing schools in different parts of the country is of course uncertain. Certainly it seems unlikely that everywhere only 1% of the entrants would come from Eire, or only 12% (36) be non-Europeans. (Most of these seemed to be concentrated in one of the smaller schools where almost the whole intake was non-European.)

For many of the students—especially those whose families already had medical or nursing associations—nursing was their career of first choice, and half had not considered another career, though over a third had qualifications which would have gained them a place in a teacher's training college. Of 256 students, 141 said they regarded nursing as a vocation, and 210 said that they would complete their training before marriage. (None were engaged at the time of the survey). Some of these answers may show the optimism and generosity of young people and will no doubt, when the completed survey is published in 1963, have to be measured against the evidence of cold figures. But if too many of these reasonably enthusiastic recruits do not finish their training, it will be another reason for reconsidering the form and content of the training.

One set of answers, however, already strikes a slightly warning note. Of 256 students, 103 plan to work (after they qualify) in hospitals abroad, and 27 hope to work with the Forces, on board ship, or as air hostesses. Clearly the remains of the group will make only a modest contribution to our own staffing problems.

HEALTH SURVEY OF LONDON OFFICE WORKERS

THOUGH the City of London has only a small resident population, it has a daily influx of half a million office workers, and the corporation is interested in the occupational health problems of those who work within its boundaries. It has therefore decided to carry out a field survey of the health of office and other workers in the City with a view to assessing the extent to which their environment is likely to comply with the legislation proposed by the Government, and whether a more or less self-supporting occupational health service would be practicable.

Surgeon Commander Alan Robinson, R.N., who is senior specialist in hygiene at Portsmouth dockyard, has been appointed to make the survey, which it is expected will take about two years.

POSTNATAL EXERCISES

A BOOKLET [1] planned by the Obstetric Association of Chartered Physiotherapists gives a clear description of some exercises designed to help a woman to regain her figure after she has had a baby. It is well illustrated by line drawings, which include arrows showing exactly where the pull in the muscles should be felt while the exercises are being done.

But many women find that their only real problem after childbirth is flabbiness of the abdominal muscles, and this is not counteracted by mild exercises such as those described in this booklet. Many mothers are advised, after the first few days, to do two other exercises, designed specifically to strengthen the abdominal muscles. These exercises are widely recommended and practised during the weeks after childbirth, and it is rather confusing to find that they are here described as "exercises to avoid" because they are harmful during the first six weeks after delivery. Is this ban really justified?

1. See *Lancet*, Sept. 23, 1961, p. 695.
2. Department of Health for Scotland. Provision and Design of Casualty and Accident Departments. H.M. Stationery Office. 1961. Pp. 34. 4*s*.
3. From Student to Nurse. 1961. Pp. 160. Obtainable from the Area Nurse Training Committee, 43, Banbury Road, Oxford. 5*s*.

1. Your Baby and Your Figure. Post-natal Exercises. Obstetric Association of Chartered Physiotherapists. Edinburgh: E. & S. Livingstone. 1961. Pp. 14. 2*s*.

University of Durham

On Sept. 23, the degree of M.D. was conferred on L. B. Strang (in absentia) and A. S. Todd.

University of Leeds

The degree of M.D. has been awarded to J. C. Woodrow.

Sir John Wolfenden will give the inaugural lecture to the faculty of medicine on Friday, Oct. 20, at 3.15 P.M. His subject will be crime and sin.

University of Glasgow

Dr. H. I. A. Nisbet has been appointed lecturer in anæsthetics and Dr. G. P. Lewis lecturer in materia medica.

International Conference on Alcohol and Road Traffic

This conference is to be held from Sept. 3 to 7, 1962, at B.M.A. House, Tavistock Square, London, W.C.1. Further particulars may be had from Dr. J. D. J. Havard, secretary of the committee of management, at B.M.A. House.

Advisory Committee on Distinction Awards

The membership of this committee for the year ending May 31, 1962, is as follows:

Lord Moran, F.R.C.P. (chairman), Sir Russell Brain, F.R.C.P. (vice-chairman), Sir Robert Aitken, F.R.C.P., A. C. H. Bell, P.R.C.O.G., H. C. Edwards, F.R.C.S., C. J. Fuller, F.R.C.P., A. Rae Gilchrist, F.R.C.P.E., Sir John Macpherson, LL.D., Sir Walter Mercer, F.R.C.S.E., A. B. Monro, M.D., D.P.M., Sir Robert Platt, P.R.C.P., Sir Arthur Porritt, P.R.C.S., Prof. C. H. Stuart-Harris, F.R.C.P., Sir Brian Windeyer, F.R.C.S., F.F.R. J. H. Wright, P.R.F.P.S., A. J. Wrigley, F.R.C.O.G.

Wellcome Trust

The trustees are to provide up to £100,000 to assist an integrated programme of research by several groups of workers into the severe anæmias prevalent in tropical countries, with special reference to the malabsorption syndrome and tropical sprue.

The trustees already support work by Dr. Henry Foy and Dr. Athena Kondi at the Medical Research Laboratories, Nairobi, Kenya, and by Dr. Selwyn Baker and others in the Wellcome Sprue Research Unit at the Christian Medical College, Vellore, South India. Dr. Foy and Dr. Kondi have worked for the Trust since 1937 as members of its staff, while the Unit at Vellore has been established and maintained by grants from the Trust since 1957. Under the new arrangements the work of both teams will be associated with that of a new Wellcome Laboratory of Tropical Hæmatology which is to be established in Prof. J. V. Dacie's department at the Postgraduate Medical School of London.

The allocation of £100,000 is made up as follows: £45,000 to build and equip the laboratory at Hammersmith; £14,000 to organise and maintain a scheme of close cooperation between the groups led by Dr. Foy, Dr. Baker, Dr. D. L. Mollin, of the Hammersmith laboratory, and an R.A.M.C. team in Singapore; £25,000, spread over five years, for the continued support of Dr. Baker's unit in Vellore; and £15,000 for new X-ray equipment at Vellore.

Other major grants out of the total of £248,000 distributed by the Trust during the last half year included:

Prof. H. E. de Wardener, £10,000 to improve the research facilities in the department of medicine at the Fulham branch of Charing Cross Hospital; Prof. F. W. Rogers Brambell, £9850 to increase the accommodation for research-workers in the department of zoology, University College of North Wales, Bangor; Dr. D. P. Cuthbertson, £10,500 to purchase new radiographic equipment for the Rowett Research Institute, Aberdeen; Dr. A. H. Harthoorn, £4000 to provide a mobile laboratory for field research in comparative physiology, University College of East Africa, Nairobi; Prof. J. D. Lever, £15,000 to purchase an electron microscope for the department of anatomy, University College of South Wales and Monmouthshire, Cardiff; Prof. D. H. R. Barton, £13,500 to purchase a nuclear magnetic resonance spectrometer, for the research programme of the department of chemistry, Imperial College of Science, South Kensington; and Prof. H. O. Schild and others, £40,000 for the extension to the pharmacology building at University College, London (already announced in July).

In the United States a five-year senior Wellcome research fellowship has been provided for Dr. Karlis Adamsons in the Columbia-Presbyterian Medical Center, New York City, at a cost of $50,000 (£18,000); his studies will be concerned chiefly with the physiology of the newborn.

Middlesex Hospital Medical School

At the school's annual dinner on Sept. 29 Mr. W. R. Winterton, the chairman, remarked that The Middlesex had suffered because it had been regarded as a modern hospital: though its bricks looked comparatively new its layout and large echoing corridors were Victorian. Nevertheless, he and Sir Brian Windeyer, the dean, were able to record substantial progress in the rebuilding of the medical school. Last year plans for the premedical and preclinical buildings had been in some jeopardy until Lord Astor, the school's "godfather", had given a further £200,000 to add to the £500,000 he had already given. Lord Astor had just completed his 40th year as a member of the board of the hospital, 23 years as chairman. His particular gift to the school, the hostel for 175 resident students, would be built as soon as the hospital could free the site. Mr. Winterton referred to the appointment of Air Vice-Marshal G. A. M. Knight as planning officer—not a "Big Brother" job but someone to reconcile the 50 different opinions of 50 consultants. The Dean's reply to the toast of The Hospital and Medical School was gracefully supported by Dr. Linda Stanton, senior Broderip Scholar. Proposing The Chairman, Prof. C. A. Keele disclosed that Mr. Winterton, obstetric and gynæcological surgeon to the hospital, was also "one of the most expert non-political bellringers in the country".

Royal Medico-Psychological Association

Prof. J. Z. Young will give a Maudsley lecture on Wednesday, Nov. 15, at 2.15 P.M., at 1, Wimpole Street, London, W.1. He will speak on memory mechanisms of the brain.

Medical Committee Against Racial Discrimination in South Africa

An open meeting of this committee will be held on Oct. 26, at 8 P.M., at B.M.A. House, Tavistock Square, London, W.C.1.

Royal College of Veterinary Surgeons

Prof. C. W. Ottaway will give a Share-Jones lecture on Tuesday, Oct. 10, at 4.45 P.M., at the Royal Veterinary College, Royal College Street, London, N.W.1. He will speak on the anatomy of motion.

Middlesex Audiology Clinics

Middlesex has two audiology units, one at Heston and one at Tottenham. Any child residing in the county who needs a full investigation of his hearing and training can be sent to these clinics through the area medical officer.

The Tottenham clinic has lately moved to a new building with a large sound-proofed and air-conditioned room especially designed for clinical examination and testing.

A new centre is being built for the Heston unit. Besides rooms for clinical examination and audiometric tests it will also have rooms for auditory training, intelligence-testing, and for making impressions for hearing-aid inserts. A staff room will also serve as an observation room with 2 one-way viewing windows. Visitors will be able to watch the clinical examinations and audiometric tests.

Demonstrations in psychiatry and neurology for doctors and senior medical students are being held at St. George's Hospital Medical School, London, S.W.1, at 5 P.M. on Thursdays until Dec. 7. The speakers will be Dr. Denis Williams, Sir Paul Mallinson, Dr. J. Hamilton Paterson, Dr. Maurice Partridge, and Prof. Desmond Curran.

The St. Thomas's Hospital old students' dinner will take place at the Savoy Hotel, London, W.C.2, on Friday, Nov. 17, at 7.30 P.M., when Dr. J. F. Ryan will be in the chair. Tickets (£2 5s.) may be had from the hon. secretary at the hospital.

A booklet on the *Part of The Family Doctor in the Mental Health Service* has been prepared by a standing committee of the Central Health Services Council. The Minister of Health is sending copies, together with some short notes on the new Act, to all general practitioners in the National Health Service.

The National Institute for the Deaf have printed 10,000 copies of the *Highway Code for Deaf Children* which will be distributed, free of charge, to all deaf and hard-of-hearing children in the country. The bulk will be sent to schools for the deaf, but copies will be sent to any deaf child or his parents who cares to write to 105, Gower Street, London, W.C.1.